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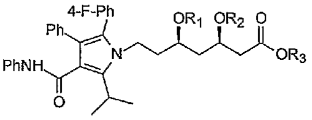
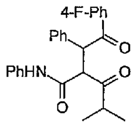
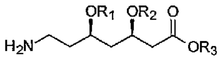
**(54) Title:** PREPARATION OF AN ATORVASTATIN INTERMEDIATE USING A PAAL-KNORR CONDENSATION







**(57) Abstract:** A process for preparing a compound of formula (I): comprises reacting a 1,4-diketone of the formula (II): with a primary amine of the formula (III): wherein $R_1$ and $R_2$ may be the same or different and are selected from any one or more of H; $C_1$-$C_6$ alkyl which may be straight or branched, substituted or unsubstituted with a halogen group; $C_1$-$C_6$ alkoxy group; or $R_1$ and $R_2$ together represent an alkylidene group of the formula $CR_aR_b$ wherein $R_a$ and $R_b$ may be the same or different and are selected from any one or more of a $C_1$-$C_{11}$ alkyl group, and $R_3$ is selected from any one or more of a $C_1$-$C_6$ alkyl group, in the presence of a catalyst, the catalyst comprising a salt wherein the salt comprises an amine salt or an inorganic salt of an organic acid.

WO 2006/097909 A1

# PREPARATION OF AN ATORVASTATIN INTERMEDIATE USING A PAAL-KNORR CONDENSATION

## Introduction

The invention relates to an improved process for preparing an intermediate used in the process for the preparation of atorvastatin.

Atorvastatin, [R–R*,R*)]–2–(4–fluorophenyl-β,δ-dihydroxy–5–(1–methylethyl)–3–phenyl–4–[(phenylamino)carbonyl]–1H–pyrrole–1–heptanoic acid, the active pharmaceutical in Lipitor™, is pharmacologically active in humans and is useful as a hypolipidemic and hypocholesterolemic agent. In particular, atorvastatin is useful as a selective and competitive inhibitor of the enzyme 3–hydroxy–3–methylglutaryl–coenzyme A (HMG–CoA) reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols such as cholesterol. The conversion of HMG-CoA to mevalonate is an early and rate-limiting step in cholesterol biosynthesis.

United States Patent Numbers 5,216,174; 5,245,047; 5,248,793; 5,397,792; 5,342,952; 5,298,627; 5,446,054; 5,470,981; 5,489,690; 5,489,691; 5,5109,488; WO97/03960; WO98/04543 and WO99/32434 which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

One manufacturing process for atorvastatin includes a Paal-Knorr condensation reaction to form an acetonide ester at the key convergent step as described in US 5,280,126, US 6,476,235 and US 6,545,153. In this reaction the complete molecular framework is assembled in good yield. However the rate of formation of the acetonide ester is low.

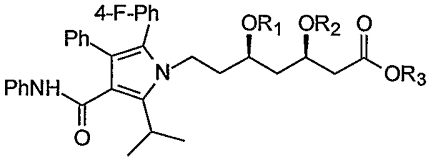
Others (Szakal et al J Org Chem 1986, 51, 621-624; Amarnath et al: J Org Chem 1991, 56 6924-6931) have tried to determine the exact working mechanism of the Paal

Knorr condensation reaction, however the mechanism is still not completely understood.

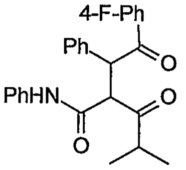
There is thus a need to optimise this rate limiting step in the preparation of atorvastatin.

Statements of Invention

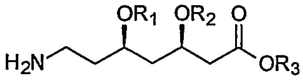
According to the invention there is provided a process for preparing a compound of formula



comprising reacting a 1,4-diketone of the formula



with a primary amine of the formula



wherein $R_1$ and $R_2$ may be the same or different and are selected from any one or more of

H,

$C_1$-$C_6$ alkyl which may be straight or branched, substituted or unsubstituted with a halogen group,

$C_1$-$C_6$ alkoxy group,

or $R_1$ and $R_2$ together represent an alkylidene group of the formula $CR_aR_b$ wherein $R_a$ and $R_b$ may be the same or different and are selected from any one or more of a $C_1$-$C_{11}$ alkyl group,

and

$R_3$ is selected from any one or more of a $C_1$-$C_6$ alkyl group,

in the presence of a catalyst, the catalyst comprising a salt wherein the salt comprises an amine salt or an inorganic salt of an organic acid.

In one embodiment of the invention $R_1$ and $R_2$ together represent isopropylidene and $R_3$ is a tertiary butyl.

The primary amine may be 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate.

In one embodiment of the invention the organic acid is a weak organic acid. The weak organic acid may have a $pKa \geq 2$.

In one embodiment of the invention the weak organic acid is any carboxylic acid having a $C_1$-$C_6$ alkyl group which may be straight or branched. The weak organic acid may be selected from any one or more of pivalic acid, formic acid, acetic acid and isobutyric acid.

In one embodiment of the invention the amine salt of the catalyst comprises a tertiary aromatic or aliphatic amine. The tertiary amine may be selected from any one or more of triethylamine ($Et_3N$), diisopropylethyl amine (DIPEA), pyridine, 1-butylimidazole or *n*-ethylmorpholine.

In one embodiment of the invention the catalyst salt is selected from any one or more of pyridine.pivalate, *n*-ethylmorpholine.pivalate, triethylamine.acetate, triethylamine.formate, triethylamine.p-toluene sulphonate, triethyamine, triethylamine.isobutyrate, triethylamine.oxalate, triethylamine.triflouroacetate, 1-butylimidazole.pivalate, 1-butylimidazole.isobutyrate, 1-butylimidazole.oxalate, 1-butylimidazole.trifluroacetate.

In another embodiment of the invention the catalyst salt is selected from any one or more of NaOAc, KOAc, $Zn(OAc)_2$, $Ca(OAc)_2$, calcium pivalate and sodium pivalate.

In one embodiment of the invention the reaction is carried out in the presence of an inert organic solvent. The inert organic solvent may be selected from Hexane:THF, MTBE:THF, and toluene. THF is tetrahydrofuran. MTBE is Methyl*tert*.Butyl Ether.

In one embodiment of the invention the reaction is carried out at a pH of greater than about pH7.

One aspect of the invention provides that the water formed during the reaction is removed azeotropically.

In one embodiment of the invention the reaction is carried out at a temperature of between 40 and 120°C.

## Detailed Description

The invention relates to an improved catalyst for the acceleration of the critical Paal-Knorr reaction. Throughput is considerably improved over the prior art.

We have discovered an improved catalyst for the Paal-Knorr reaction to prepare the critical atorvastatin intermediate tert-butyl 2-((4R,6S)-6-((3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate. It has been found that the addition of an amine to an organic acid currently used to catalyse the reaction, affords a dramatically shorter reaction time as well as an improved yield.

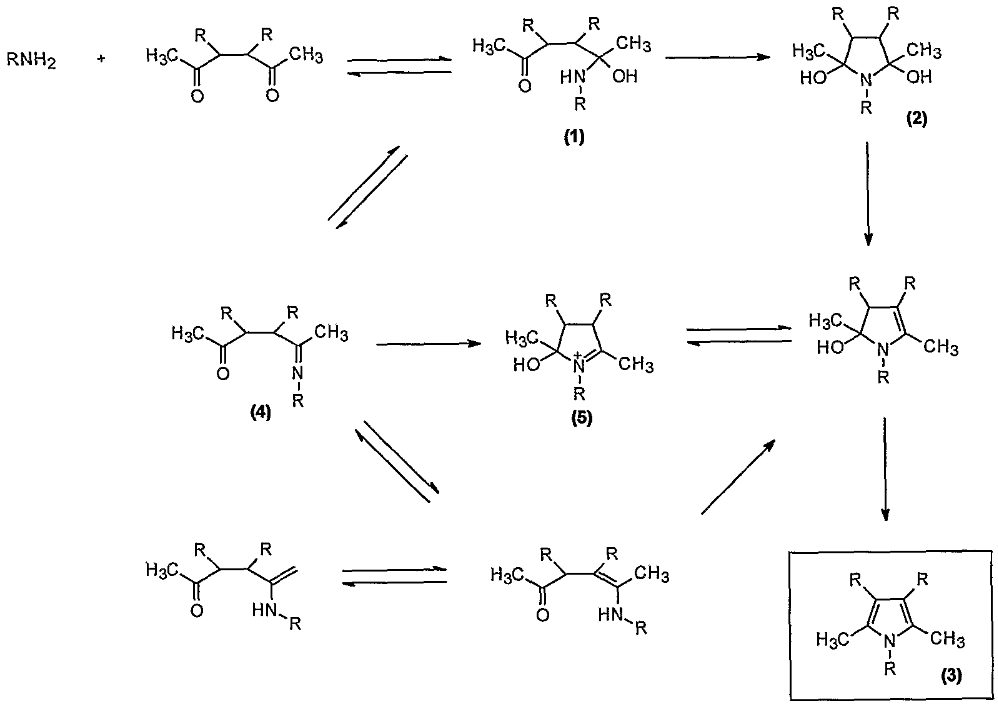
The invention will be more clearly understood from the following description thereof given by way of example only.

The present invention provides an improved process for preparing the acetonide ester of atorvastatin (tert-butyl 2-((4R,6S)-6-((3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate). The acetonide ester is prepared with improved throughput with an increased reaction rate, high yield and a high level of purity.

The current process for preparing the acetonide ester of atorvastatin is carried out using a Paal Knorr reaction by reacting the diketone of atorvastatin, 4-fluoro- (2-methyl-1-oxopropyl-γ-oxo-*N*-β-diphenyl-benzenebutaneamide with the primary amine, 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate. The reaction is carried out in the presence of an acid catalyst in an inert solvent. Full details of the reaction are given in US5,280,126, US6,476,235 and US6,545,153.

Neither the precise mechanism of the Paal-Knorr reaction nor the identity of the rate-determining step is known although studies have shed light on the presumed mechanistic pathway (Szakal et al, J Org Chem 1986,51,621-624). Scheme 1 below taken from Amarnath et al (J. Org. Chem. 1991, 56 6924-6931) shows a proposed mechanism of the reaction.

Scheme 1



The proposed mechanism involves the addition of the amine component to one of the carbonyl carbons to form a hemiaminal (1). Intramolecular attack on the second carbonyl affords a diol (2), which must eliminate water (x2) to form a pyrrole (3).

Alternatively, attack at one carbonyl and elimination of water leads to the formation of an imine (4), which can then form a pyrrole (3) via enamines and water elimination.

Irrespective of the path chosen, the rate determining step appears to be the cyclisation to form either the diol (2) or the quaternary iminium salt (5). The Paal Knorr transformation is acid catalysed. In the case of Atorvastatin, the pyrrole ring formation of the acetonide ester is a key rate limiting step.

In the present invention it has been found that both a significant rate enhancement and higher yield can be obtained by addition of a tertiary amine to the Paal-Knorr reaction mixture. The quality of the acetonide ester produced by the improved process is at least comparable to that produced by the prior art process.

The catalyst salts of the invention were surprisingly found to work efficiently in a wide range of solvents of varying polarity. The catalyst salts were found to work efficiently in organic solvents, which solvents are important for water removal and solubility of the reactants. Optimal solvent combinations for the improved process are mixtures of MTBE:THF and Hexane:THF. However, solvents may be selected from any one or more of toluene or other aromatic hydrocarbons, THF, or other cyclic and acyclic ethers, ethyl acetate and other esters of alcohols with carboxylic acids, 2-butanone, MIBK and other cyclic and acyclic ketone, methanol and other alcohols, IPA, acetonitrile, DMSO, DMF and other amides, hexane, heptane, and other acyclic and cyclic aliphatic hydrocarbons. Aliphatic nitriles may also be used as solvents. Binary mixtures of the above may also be used such as 1,4-dioxane:MTBE, 1,4-dioxane:Hexane, hexane:acetonitrile, 1,4-dioxane:methylcyclohexane, 1,4-dioxane:cyclohexane, DME:hexane.

The catalyst salt may be comprised of an amine salt of an organic acid or an inorganic salt of an organic acid or an organic salt of an inorganic acid. The acid may be a weak or strong acid.

The weak organic acid having a pKa ≥ 2 and may be selected from but is not limited to any one of pivalic acid, formic acid, acetic acid or isobutyric acid.

A strong acid having a pKa ≤ 2 may also be selected from but is not limited to any one or more of *p*-toluene sulphonic acid, oxalic acid, trifluoroacetic acid, sulphuric acid or hydrochloric acid.

The amine of the catalyst may be a tertiary amine or a sterically hindered secondary amine. The tertiary amine may be selected from, but is not limited to any one or more of aromatic or aliphatic amines such as, pyridine, *N*-ethylmorpholine, diisopropylethylamine, triethylamine or 1-butylimidazole or N,N-dimethylaniline.

The salt catalyst may be selected from but is not limited to any one or more of pyridinium.pivalate, *n*-ethylmorpholine.pivalate, triethylammonium.acetate, triethylammonium.formate, triethylammonium.p-toluene-sulphonate, triethylammonium.pivalate, triethylammonium.isobutyrate, triethylammoniium.oxalate, triethylammonium.triflouroacetate, 1-butylimidazolium.pivalate, 1-butylimidazolium.isobutyrate, 1-butylimidazolium.oxalate, 1-butylimidazolium.trifluroacetate.

The Paal Knorr condensation reaction results in the formation of water and the presence of water may have a detrimental effect on the overall reaction rate. The salt catalysts of the invention are non-volatile and allow for easy and efficient removal of the water by distillation without removing or affecting the catalyst activity which is important for high yield.

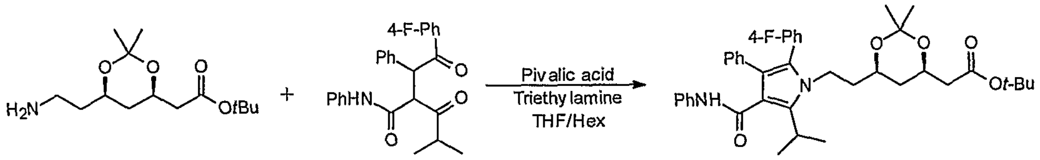
The reaction is carried out in the presence of an organic solvent which also provides for the removal of water formed during the condensation reaction.

The reaction may be carried out in less than 90 hours and the process of the present invention results in a 20% reduction in reaction time over the processes described in Wade et al, Organic Research Process and Development, 1997, 1, 320-324.

The invention will be more clearly understood by the following examples. The catalyst may be prepared in situ as described in the following examples. Alternatively, the catalyst can be prepared by mixing equimolar amounts of the acid and base. The product of this reaction can then be used in the process.

Example 1: Triethylammonium pivalate as catalyst; hexane: THF as solvent

Schematic:



Diketone of atorvastatin (1.09 eq, 84.4g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate [TBIN] (50.69g, 185.4 mmol) in THF (112.6 g) and hexane (42.7 g) and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C pivalic acid (0.7 eq, 13.3g) is added, followed by triethylamine (0.7 eq., 13.2 g) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

On completion the reaction mixture is cooled to 25°C before addition of MTBE (157 g). The solution is washed with a 5.5 % (w/w) solution of KOH, then a 3.5 % (w/w) of HCl, separated and then the organic layer is vacuum distilled with stirring to a thick oil. At the distillation end-point acetone (100 ml) and IPA (100ml) were added and the mixture was heated to 50°C until a solution is achieved. Water (50ml) was added to the solution and the mixture was allowed to cool to room temperature over two hours, then cooled to 0°C and stirred for 1 hr. The crystals were isolated by filtration and washed with IPA (50ml at 0°C). The product was dried in a vacuum oven maintaining the temperature at <40°C.

Example 2: Triethylammonium pivalate as catalyst; MTBE: THF as solvent

Diketone of atorvastatin (1.09 eq, 84.4g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (50.69g, 185.4 mmol) in THF (57.7 g) and MTBE (99.4 g) and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C pivalic acid (0.7 eq, 13.3g) is added, followed by triethylamine (0.7 eq., 13.2 g) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

On completion the reaction mixture is cooled to 25°C before addition of MTBE (157 g). The solution is washed with a 5.5 % (w/w) solution of KOH (230 ml), then a 3.5 % (w/w) of HCl (250 ml), separated and then the organic layer is vacuum distilled with stirring to a thick oil. At the distillation end-point acetone (100 ml) and IPA (100ml) were added and the mixture was heated to 50°C until a solution is achieved. Water (50ml) was added to the solution and the mixture was allowed to cool to room temperature over two hours, then cooled to 0°C and stirred for 1 hr. The crystals were isolated by filtration and washed with IPA (50ml at 0°C). The product was dried in a vacuum oven maintaining the temperature at <40°C.

Example 3: *N*-ethylmorpholine pivalate as catalyst; Toluene as solvent

Diketone of atorvastatin (1.09 eq, 8.32 g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (5.0g, 18.3 mmol) in Toluene (13 g) and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C pivalic acid (0.7 eq, 1.15 g) is added, followed by n-ethylmorpholine (0.7 eq., 1.47 g) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

Example 4: Diisopropylethylammonium pivalate as catalyst; toluene as solvent

Diketone of atorvastatin (1.09 eq, 8.32 g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (5.0g, 18.3 mmol) in Toluene (13 g) and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C pivalic acid (0.7 eq, 1.15 g) is added, followed by diisopropylethylamine (0.7 eq., 1.65 g) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water

Example 5: Zinc acetate as catalyst; MTBE:THF as solvent

Diketone of atorvastatin (1.09 eq, 8.3g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (5.0g, 18.5 mmol) in THF (5.7 g) and MTBE (6.7g). Zinc acetate (1.59g, 12.9 mmol) is added and the resulting suspension then heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

Example 6: Sodium pivalate as catalyst; MTBE:THF as solvent

Diketone of atorvastatin (1.09 eq, 8.32 g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (5 g, 18.3 mmol) in THF (5.3 g) and MTBE (6.7g). and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C pivalic acid (0.7 eq, 0.34g) is added, followed by 50% sodium hydroxide (1 g, 12.5 mmol) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

Example 7: Calcium pivalate as catalyst; MTBE:THF as solvent

Diketone of atorvastatin (1.09 eq, 8.32 g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (5 g, 18.3 mmol) in THF (5.3 g) and MTBE (6.7g). and the mixture warmed to 50°C under an $N_2$ atmosphere.

At 50°C pivalic acid (0.7 eq, 1.15g) is added, followed by calcium hydroxide (0.47 g, 6.35mmol) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

<u>Example 8</u>: Sodium pivalate as catalyst; Toluene as solvent

Diketone of atorvastatin (1.09 eq, 5.03 g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (3 g, 10.9 mmol) in toluene (8.65g) and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C pivalic acid (0.7 eq, 0.69g) is added, followed by 50% sodium hydroxide (0.61 g, 7.6 mmol) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

<u>Example 9</u>: Triethylammonium hydrochloride as catalyst; MTBE:THF as solvent

Diketone of atorvastatin (1.09 eq, 8.32 g) is added to a solution of 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (5 g, 18.3 mmol) in MTBE (6.7g) and THF (5.4 g) and the mixture warmed to 50°C under an $N_2$ atmosphere. At 50°C triethylamine (0.7 eq, 1.29g) is added, followed by 36% hydrogen chloride (0.7 eq, 1.30 g) and the resulting suspension heated at reflux under a nitrogen atmosphere until reaction completion, with concomitant removal of water.

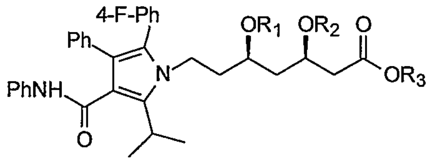
High yield is critical in this late stage of the process when all the functionality of the active pharmaceutical ingredient, including two chiral centres are essentially in place and this invention thus ensures a major cost benefit. The current process with long reaction times (>100 hours for the Paal-Knorr reaction) is a major bottleneck in throughput and is a significant consumer of energy since continuous heating is required. The preferred embodiment of the invention (amine salt of an organic acid) gives a 3% increase in yield and 20% reduction in reaction time vs. the current process. Because the present invention increases throughput and thus capacity it has the added benefit of saving energy.

The process of the invention gives consistently higher yields and much reduced cycle times for the Paal-Knorr cyclisation reaction. These improvements enable considerably more efficient usage of plant during production of atorvastatin. The invention is particularly useful in factory scale production in which reductions in reaction time and improvements in yield are economically very significant.

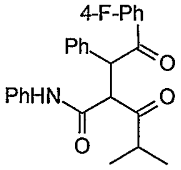
The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

Claims

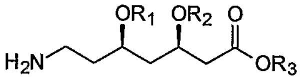
1. A process for preparing a compound of formula



comprising reacting a 1,4-diketone of the formula



with a primary amine of the formula



wherein $R_1$ and $R_2$ may be the same or different and are selected from any one or more of

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$C_1$-$C_6$ alkyl which may be straight or branched, substituted or unsubstituted with a halogen group,

$C_1$-$C_6$ alkoxy group,

or $R_1$ and $R_2$ together represent an alkylidene group of the formula $CR_aR_b$ wherein $R_a$ and $R_b$ may be the same or different and are selected from any one or more of a $C_1$-$C_{11}$ alkyl group,

and

$R_3$ is selected from any one or more of a $C_1$-$C_6$ alkyl group, in the presence of a catalyst, the catalyst comprising a salt wherein the salt comprises an amine salt or an inorganic salt of an organic acid.

2. A process as claimed in claim 1 wherein $R_1$ and $R_2$, together represent isopropylidene and $R_3$ is a tertiary butyl.

3. A process as claimed in claim 1 or 2 wherein the primary amine is 1,1-dimethyl-(4R-*cis*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate.

4. A process as claimed in any of claims 1 to 3 wherein the organic acid is a weak organic acid.

5. A process as claimed in claim 4 wherein the weak organic acid has a $pKa \geq 2$.

6. A process as claimed in claim 4 or 5 wherein the weak organic acid is any carboxylic acid having a $C_1$-$C_6$ alkyl group which may be straight or branched.

7. A process as claimed in any of claims 4 to 6 wherein the weak organic acid is selected from any one or more of pivalic acid, formic acid, acetic acid and isobutyric acid.

8. A process as claimed in any of claims 1 to 7 wherein the amine salt of the catalyst comprises a tertiary aromatic or aliphatic amine.

9. A process as claimed in claim 8 wherein the tertiary amine is selected from any one or more of triethylamine ($Et_3N$), diisopropylethyl amine (DIPEA), pyridine, 1-butylimidazole, and *n*-ethylmorpholine.

10. A process as claimed in any of claims 1 to 9 wherein the catalyst salt is selected from any one or more of pyridine.pivalate, *n*-ethylmorpholine.pivalate, triethylamine.acetate, triethylamine.formate,

triethylamine.p-toluene sulphonate, triethyamine, triethylamine.isobutyrate, triethylamine.oxalate, triethylamine.triflouroacetate, 1-butylimidazole.pivalate, 1-butylimidazole.isobutyrate, 1-butylimidazole.oxalate, and 1-butylimidazole.trifluroacetate.

11. A process as claimed in any of any of claims 1 to 9 wherein the catalyst salt is selected from any one or more of NaOAc, KOAc, $Zn(OAc)_2$, $Ca(OAc)_2$, calcium pivalate and sodium pivalate.

12. A process as claimed in any of any of claims 1 to 11 wherein the reaction is carried out in the presence of an inert organic solvent.

13. A process as claimed in claim 12 wherein the inert organic solvent is selected from Hexane:THF, MTBE:THF and toluene.

14. A process as claimed in any of claims 1 to 13 wherein the reaction is carried out at a pH greater than about pH 7.

15. A process as claimed in any of claims 1 to 14 wherein the water formed during the reaction is removed azeotropically.

16. A process as claimed in any of claims 1 to 15 wherein the reaction is carried out at a temperature of between 40 and 120°C.

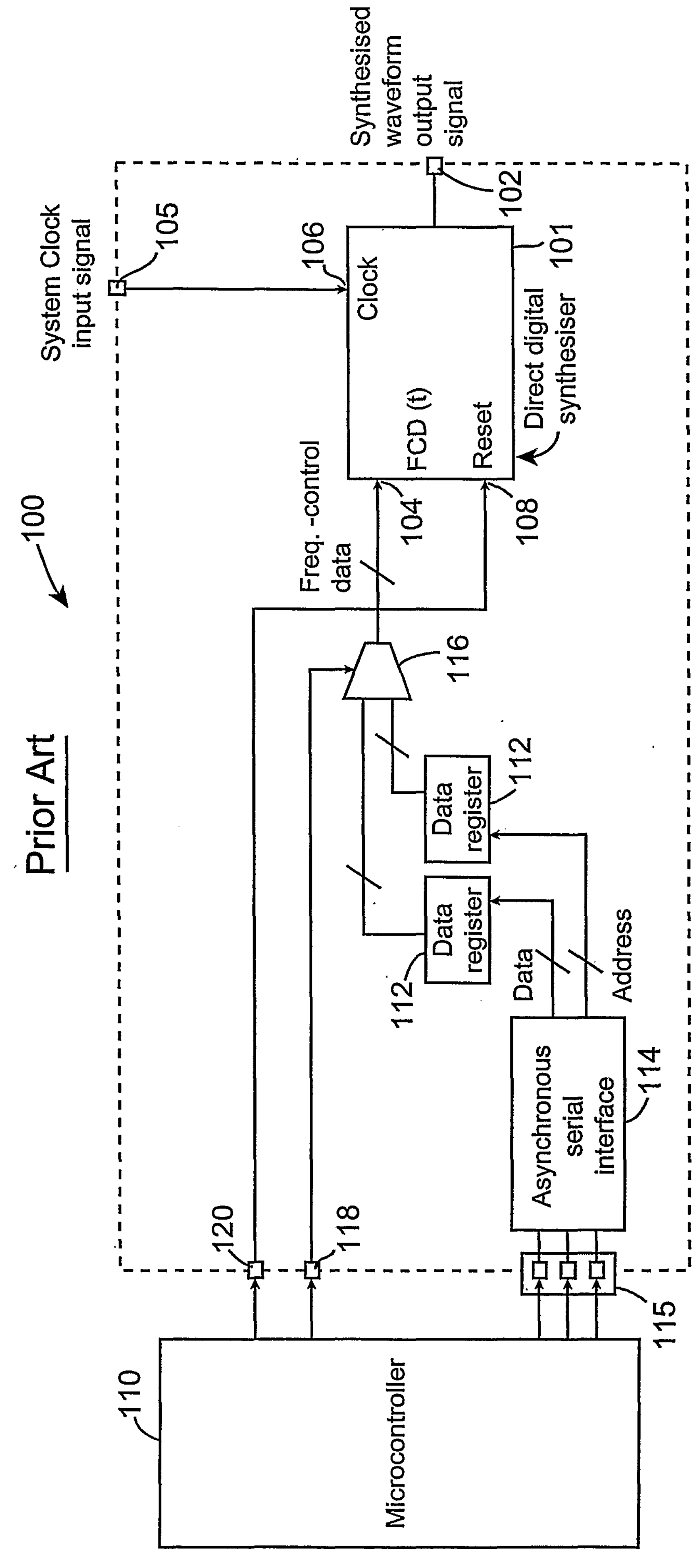
Prior Art
100
System Clock input signal
105
106
Clock
Synthesised waveform output signal
102
101
Direct digital synthesiser
FCD (t)
Reset
104
108
Freq. -control data
116
Data register
112
Data register
112
Data
Address
Asynchronous serial interface
114
120
118
115
Microcontroller
110

Fig. 1

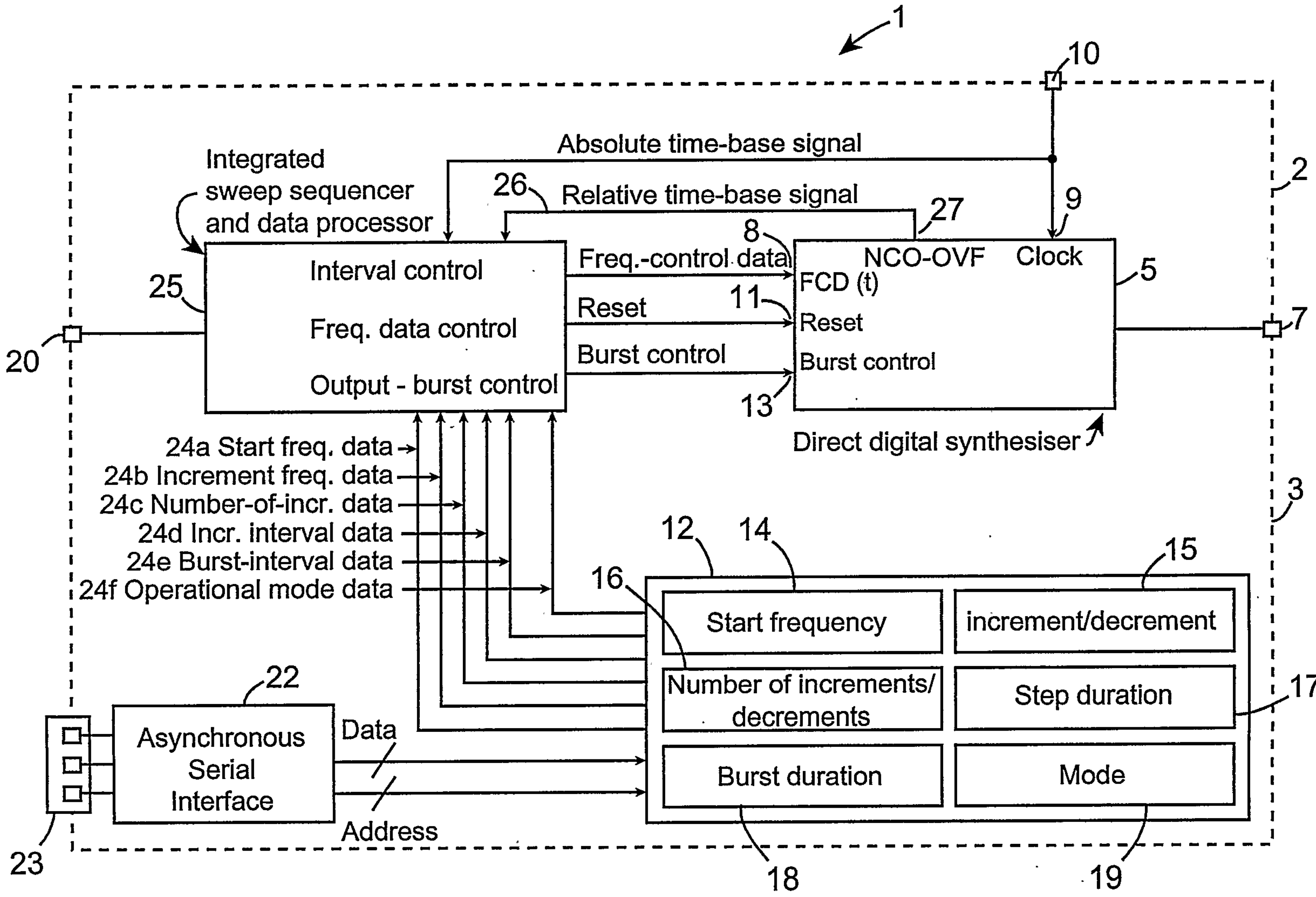
1
10
Absolute time-base signal
Integrated sweep sequencer and data processor
26
Relative time-base signal
27
9
2
8
Freq.-control data
NCO-OVF
Clock
25
Interval control
FCD (t)
5
Freq. data control
Reset
11
Reset
20
Burst control
Burst control
7
Output - burst control
13
Direct digital synthesiser
24a Start freq. data
24b Increment freq. data
24c Number-of-incr. data
24d Incr. interval data
24e Burst-interval data
24f Operational mode data
3
12
14
15
16
Start frequency
increment/decrement
22
Number of increments/ decrements
Step duration
17
Asynchronous Serial Interface
Data
Burst duration
Mode
Address
23
18
19

Fig. 2

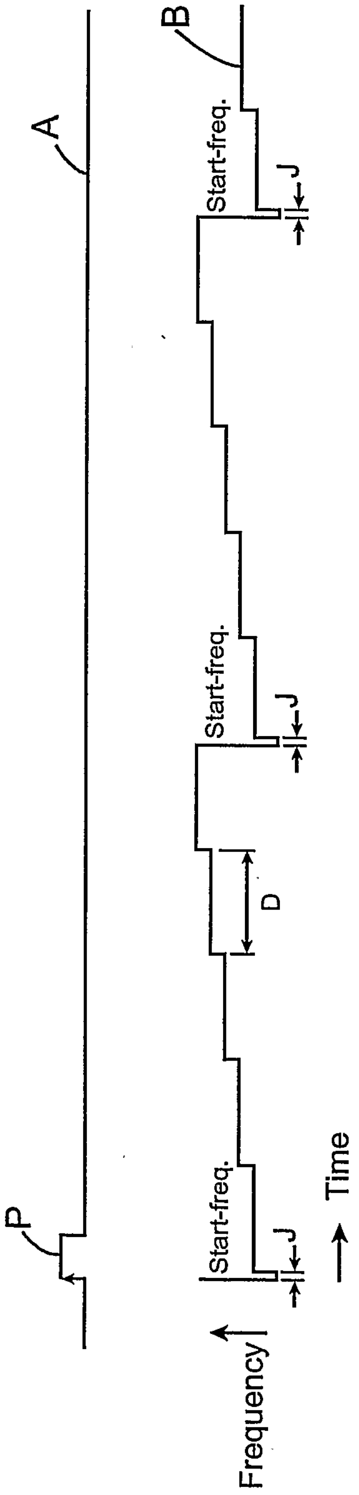

Fig. 3

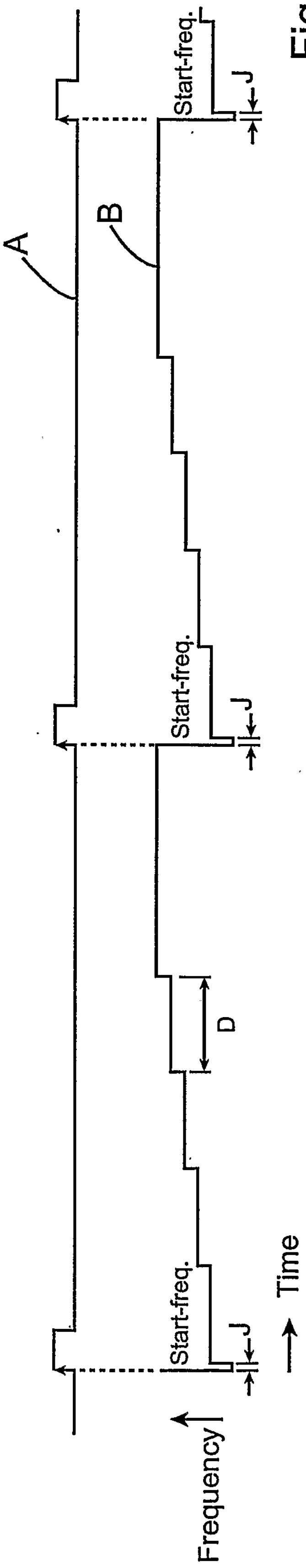

Fig. 4

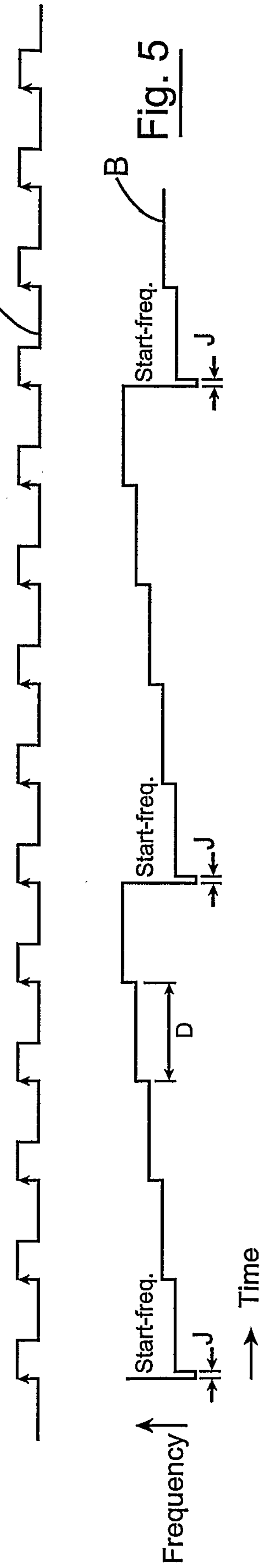

Fig. 5

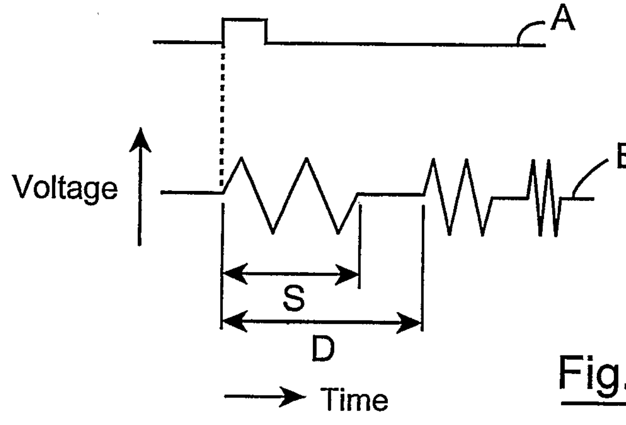

Fig. 6

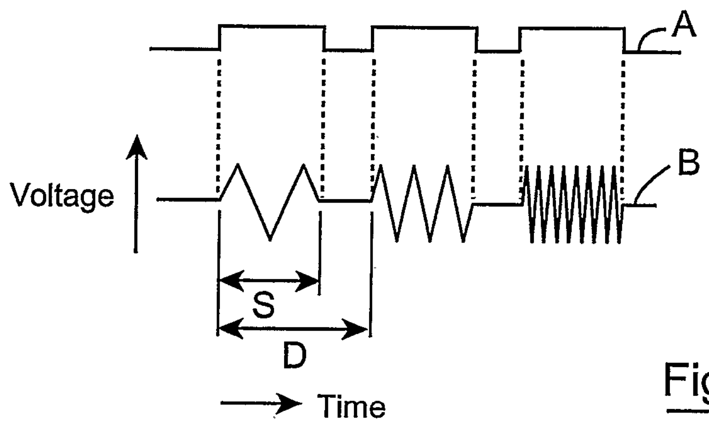

Fig. 7

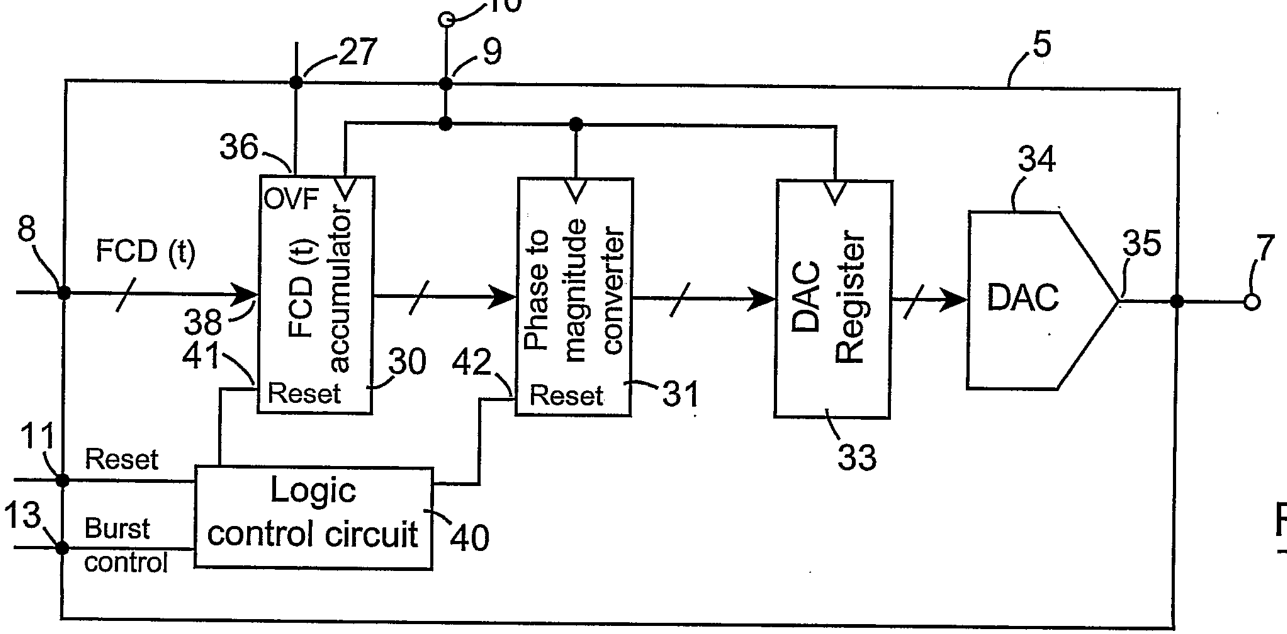

Fig. 8

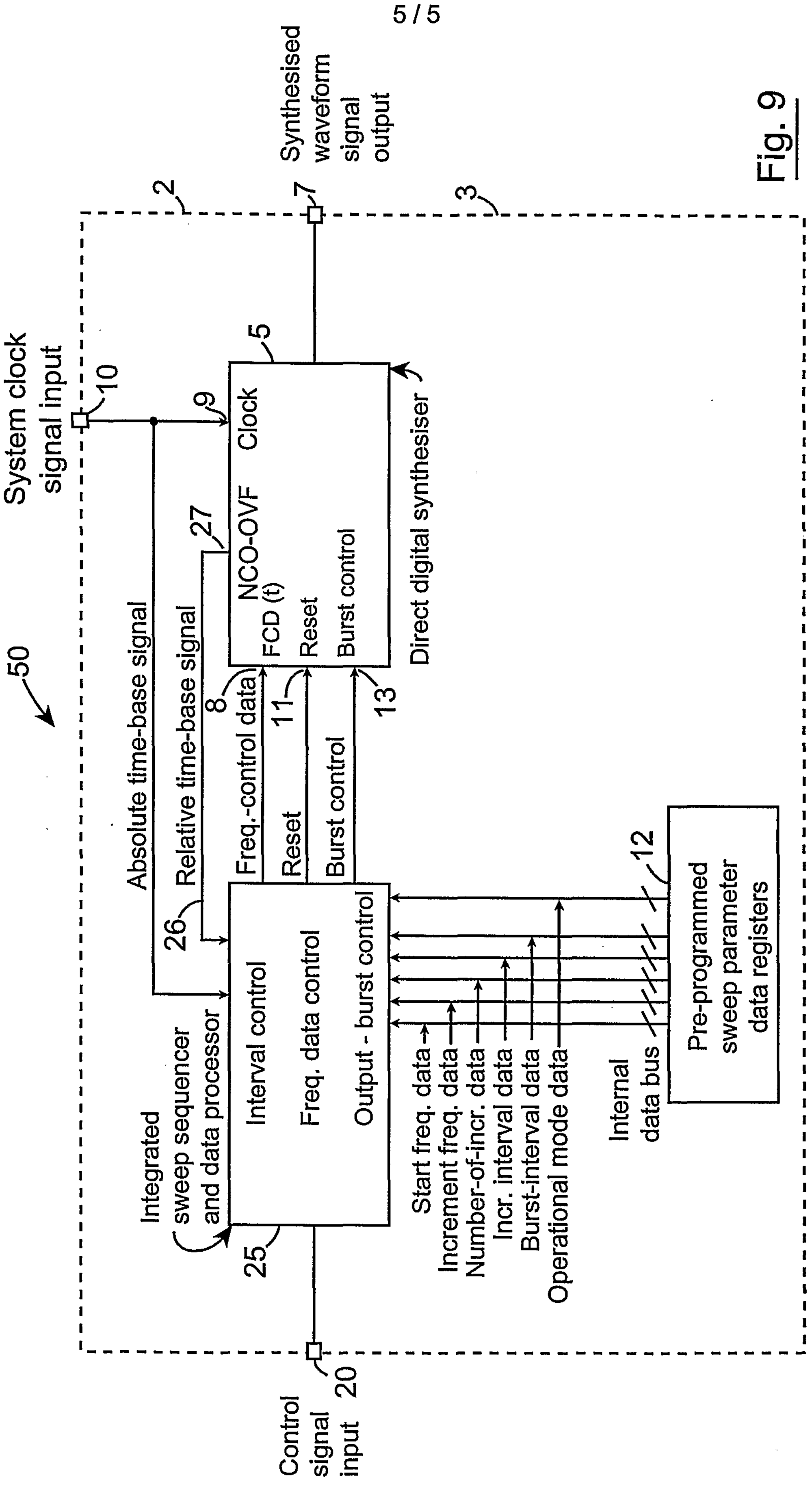
50
System clock signal input
10
9
Clock
5
Synthesised waveform signal output
7
2
3
NCO-OVF
FCD (t)
Reset
Burst control
Direct digital synthesiser
27
Absolute time-base signal
Relative time-base signal
8
11
13
Freq.-control data
Reset
Burst control
26
Integrated sweep sequencer and data processor
Interval control
Freq. data control
Output - burst control
25
Start freq. data
Increment freq. data
Number-of-incr. data
Incr. interval data
Burst-interval data
Operational mode data
Internal data bus
12
Pre-programmed sweep parameter data registers
Control signal input
20

Fig. 9

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IE2006/000014

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/32

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)
C07D

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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<br>28 April 2006 | Date of mailing of the international search report<br>18/05/2006 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>Bérillon, L |

## INTERNATIONAL SEARCH REPORT

International application No
PCT/IE2006/000014

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