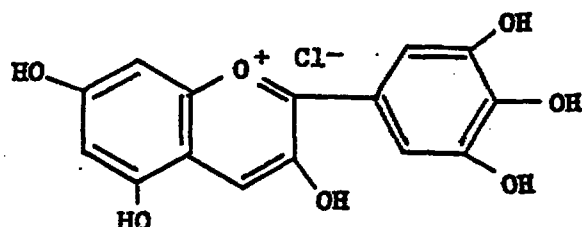


Description

This invention relates to a process for synthesizing delphinidin and its salts, to a novel group of intermediates formed during the synthesis and to novel procedures for producing the intermediates.

Delphinidin is a member of the class of substances known as anthocyanidins. Its chloride has the following structure

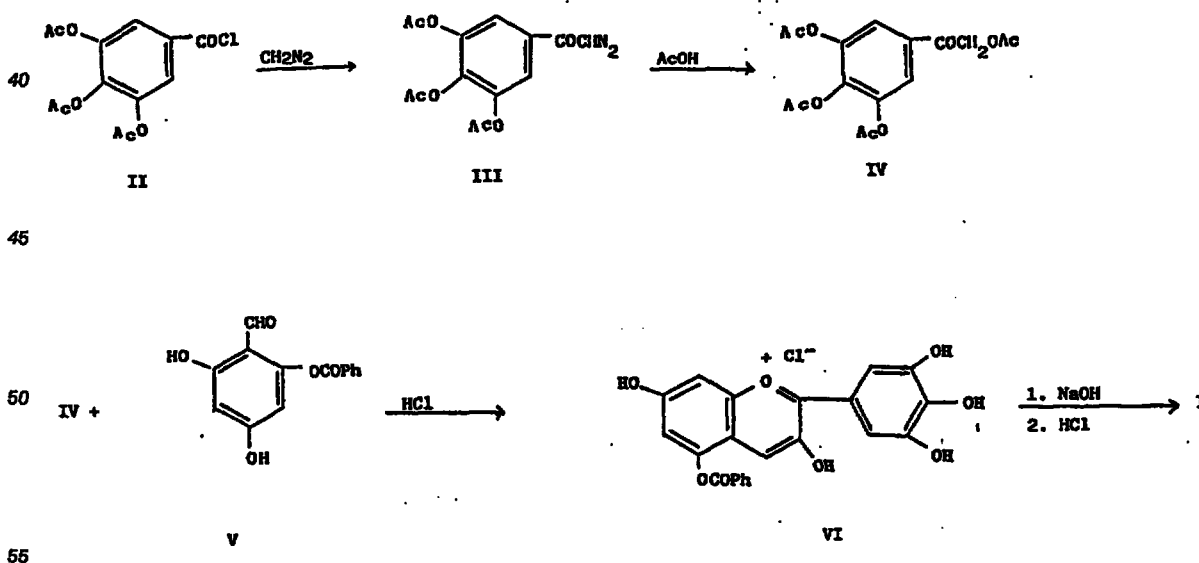


I

Anthocyanidins are polyphenolic substances which are widely distributed in nature in the form of glycosides known as anthocyanins, and as such are largely responsible for the colouring of fruits and flowers. Anthocyanidins are endowed with remarkable cicatrizing or healing properties and moreover possess anti-inflammatory, vasoprotective, hypolipæmic, hypocholesterolaemic and hypoglycaemic activity. Their pharmaceutical use in these areas has been described and claimed in our earlier patents (GB 1589294 and GB 1595351; Inverni Della Beffa SpA, Milan). Amongst the anthocyanidins, delphinidin is one of the most widespread in nature and pharmacologically most active.

Delphinidin can be obtained by hydrolysis of its glycosidic derivatives, by semi-synthesis from natural substances containing a suitably substituted flavone nucleus, or by complete synthesis by Robinson's method (W. Bradley, R. Robinson and G. Schwarzenbach, J. Chem. Soc., 793, 1930). The known procedure for the complete synthesis of delphinidin is illustrated in Scheme 1. This procedure involves the reaction of triacetylalloyl chloride (II) with diazomethane. The resulting diazoketone (III) is then transformed by acetolysis into ω -acetoxy-3,4,5-triacetoxyacetophenone (IV), which is condensed with the benzoate (V) in acidic medium to give the protected delphinidin (VI). Delphinidin chloride (I) may be obtained from VI means of basic hydrolysis and subsequent acidification with hydrochloric acid.

Scheme 1



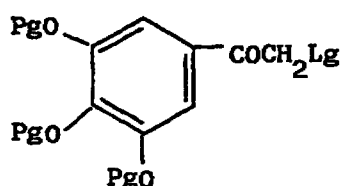
All the known methods, however, are difficult to carry into effect on an industrial scale. Semi-synthesis from natural flavonoid synthons is inconvenient, because of the difficulties of finding the necessary

quantities of starting materials in nature, and Robinson's synthesis has drawbacks for reasons of safety. In fact, the preparation of the intermediate IV by the procedure of Scheme 1 requires the use of diazomethane, a reagent with characteristics of toxicity and explosiveness which discourage its use on a large scale.

An object of the present invention is to provide a novel procedure for the preparation of intermediate IV and related compounds which utilizes reactants and operating conditions which are readily transferable to an industrial scale and results in the production of this intermediate in high yields and in a state of high chemical purity.

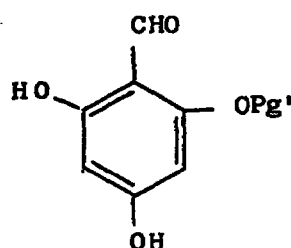
The process of the invention according to one aspect thereof is based on the realisation that a superior procedure for synthesising delphinidin and its salts involves the synthesis of 3,4,5-trihydroxyacetophenone as an intermediate. As will be described below, 3,4,5-trihydroxyacetophenone can itself be produced by a novel procedure which avoids drawbacks of known processes and can be converted to compound IV in Scheme 1 or related compounds.

According to one aspect of the invention there is provided a process for producing delphinidine which comprises reacting a compound of formula



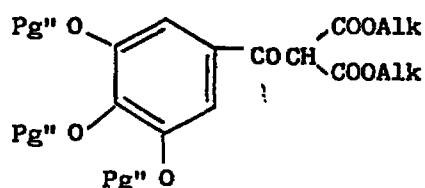
VII

wherein each Pg represents a hydroxyl protecting group and Lg represents an acyloxy group with a compound of formula



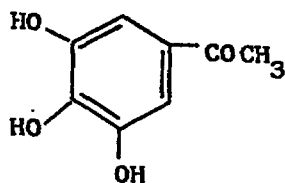
VIII

wherein Pg' represents a hydroxyl protecting group characterised in that the compound of formula VII is produced from an intermediate of formula



IX

wherein each Pg'' represents a hydroxyl protecting group and each Alk represents lower alkyl, by
(i) subjecting the intermediate of formula IX to hydrolysis and decarboxylation to form 3,4,5-trihydroxyacetophenone of formula

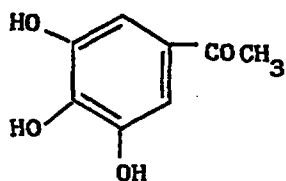


X

(ii) converting the 3,4,5-trihydroxyacetone to the compound of formula VII by introduction of the protecting groups Pg and converting the group of formula $-\text{COCH}_3$ to a group of formula $-\text{COCH}_2\text{Lg}$.

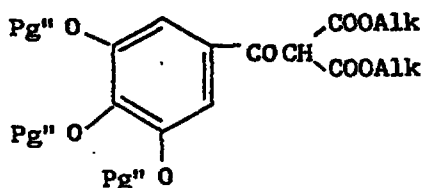
The compounds of formula IX are novel and form a further aspect of the invention, as do certain novel processes for their production and conversion to 3,4,5-trihydroxyacetophenone.

Thus according to a further aspect of the process of the present invention the 3,4,5-trihydroxyacetophenone (X)



X

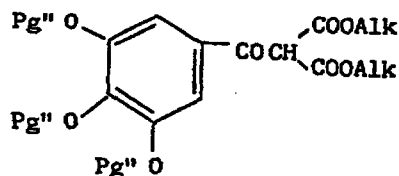
is preferably produced by subjecting a compound of formula



IX

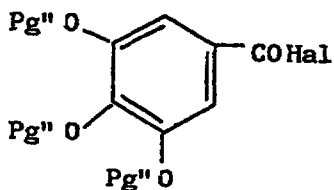
in which each Pg'' represents a hydroxyl protecting group and each Alk represents lower alkyl, to hydrolysis and decarboxylation.

The compound of formula (IX)



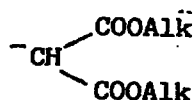
IX

is preferably produced by reacting a compound of formula (XI)



XI

wherein Pg'' represents a hydroxyl protecting group and Hal represents halogen, particularly chlorine, with a source of carbanions of formula (XII) derived from a di-loweralkyl malonate



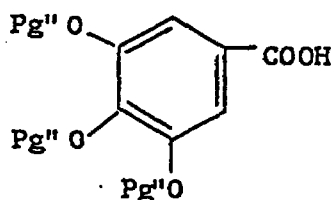
XII

In the above formulae the protecting groups Pg and Pg' and Pg'' may be any known protecting group of the hydroxyl function which is stable under the reaction conditions employed, either in producing the intermediate in question or in its subsequent conversion. Thus, for example, the groups Pg, Pg' and Pg'' may be a carboxylic acid acyl group derived from, for example, a C₁₋₆ aliphatic carboxylic acid, e.g. acetic acid, propionic acid, butyric acid etc or a C₆₋₁₀ aromatic carboxylic acid, e.g. benzoic acid. Alternatively, Pg, Pg' and Pg'' may be derived from a sulphonic acid, e.g. toluene sulphonic acid or benzene sulphonic acid.

Preferably, the protecting groups Pg and Pg'' are acetyl and the protecting group Pg' is benzoyl. Lg preferably is a C₁₋₆ carboxylic acid acyloxy group, most preferably acetoxy.

Alk may be any straight or branched chain lower alkyl group, but preferably is methyl or ethyl. Hal is preferably chlorine.

The starting material of formula (XI) may be produced by conventional procedures, e.g. by esterifying 3,4,5-trihydroxybenzoic acid so as to introduce protecting groups Pg'', followed by reaction of tri-ester

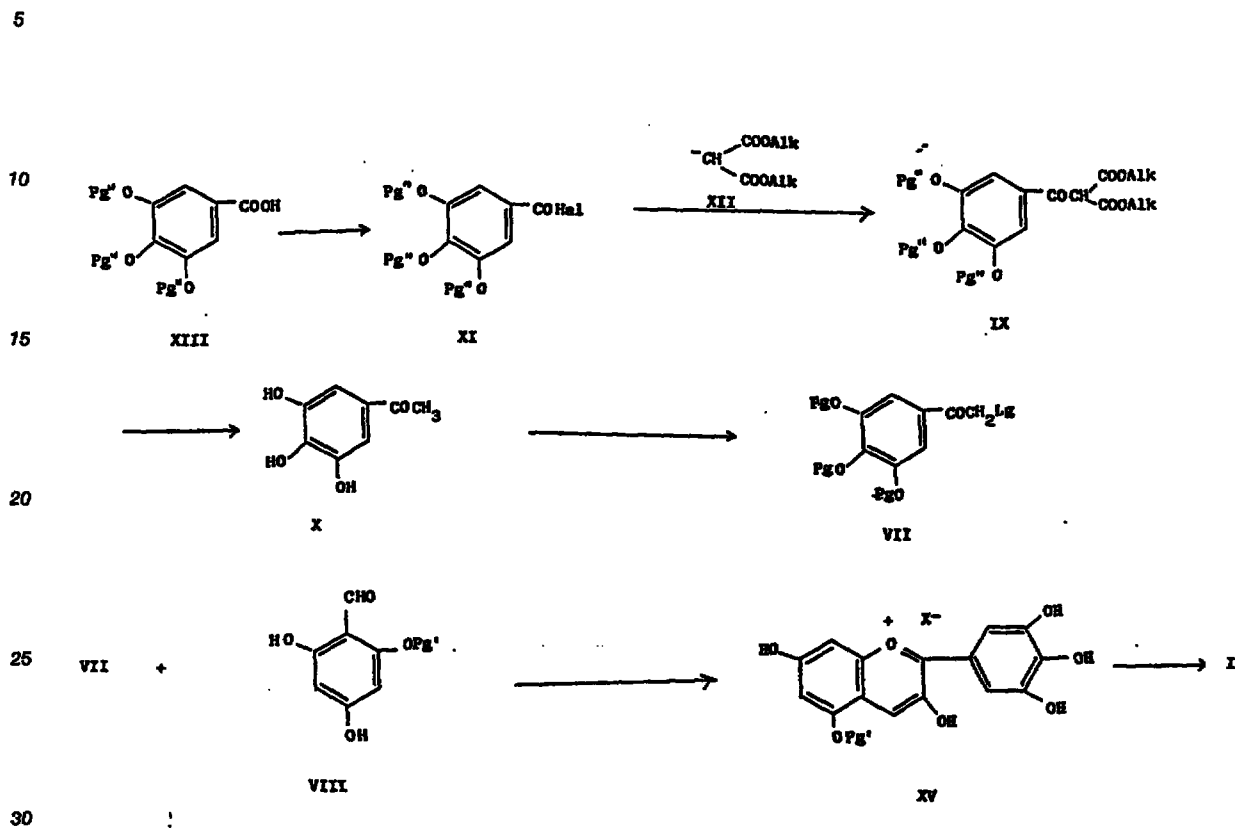


(XIII)

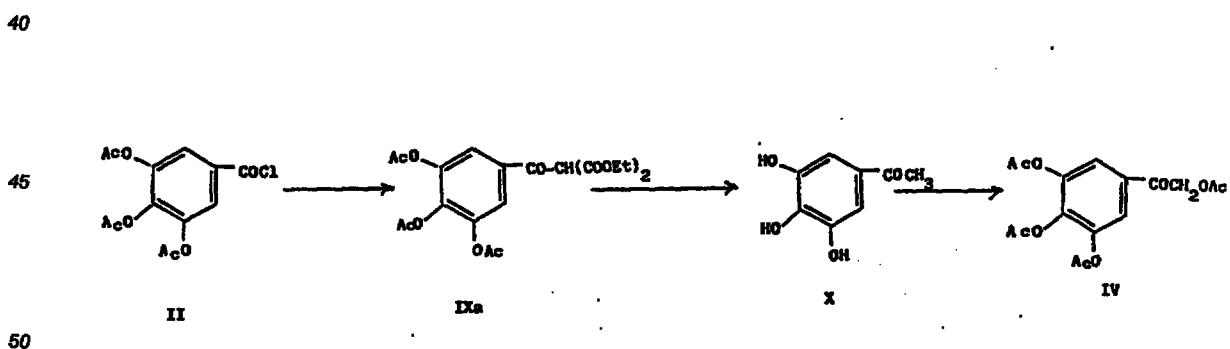
with a halogenating agent, e.g. PCl₅ or SOCl₂.

The process of the invention may be illustrated by the following Schemes 2 and 3, where Scheme 2 represents the procedures of the invention expressed in terms of general formulae and Scheme 3 represents, by way of example, reactions of specific compounds.

SCHEME 2



SCHEME 3



In Scheme 3, the chloride of triacetyl gallic acid (II), which may be obtained by known synthesis procedures, may be reacted with ethyl ethoxymagnesium malonate, preparing *in situ* by reaction between magnesium, ethanol and diethyl malonate, in an aprotic solvent (for example, tetrahydrofuran), to give the novel compound ethyl 3,4,5-triacetoxybenzoylmalonate (IXa). This, which need not necessarily be isolated, is hydrolyzed by heating at 70-100°C in an acid medium and, after decarboxylation of the malonic residue, supplies directly the methyl ketone X.

The desired intermediate IV may be obtained from X via a "one pot" synthetic process in which the protection of the phenolic functions as acetates is effected by heating compound X at 30-50 °C in acetic anhydride containing sulphuric acid as catalyst, ω -bromination and nucleophilic substitution of the bromine with potassium acetate carried out at 90-110 °C.

The product IV can thus be prepared advantageously in only two synthesis operations (XIa→X→IV) without isolation of the intermediate products.

Compared with the method proposed by Robinson, the procedure of the invention, in addition to utilizing reactants which are free from danger in use, presents the advantage of enabling intermediate IV to be obtained from starting material II with higher yields (80% instead of 65%) and in a high degree of purity. This last advantage, in fact, is a necessary condition for the preparation of delphinidin chloride free from by-products which cannot be eliminated from the final product by the normal methods of purification.

For the preparation of delphinidin chloride, IV may be condensed with phloroglucinaldehyde which has been suitably protected on the phenolic functions (for example, the 2-O-benzoate V).

After removal of the protecting groups, delphinidin chloride may be obtained in pure form and in high yields (80% from IV), without it being necessary to carry out the laborious purification operations required during Robinson's synthesis.

The following Examples illustrate the invention without limiting it.

EXAMPLE 1

Synthesis of ethyl 3,4,5-triacetoxybenzoylmalonate (IXa)

A suspension of 580 g of magnesium turnings, 100 ml of carbon tetrachloride and 4 l of anhydrous tetrahydrofuran is reacted in an inert atmosphere with 520 ml of absolute ethanol. The reaction mixture is diluted with tetrahydrofuran and a suspension of 3.6 l of diethyl malonate and 860 ml of absolute ethanol is added. When dissolution has taken place, 6.7 kg of the acid chloride of triacetyl gallic acid (II) suspended in tetrahydrofuran are added and the reaction mixture is kept at reflux with agitation for one hour. The reaction mixture is diluted with ethyl acetate and with a solution of dilute sulphuric acid.

The organic phase is separated, washed with water, dried and concentrated to a small volume. By dilution of the residue with isopropyl ether, IXa crystallizes and is recovered by filtration and dried.

8.96 kg of IXa are obtained (yield: 96%), m.p. 99-100 °C, M^+ at m/z 438.

Found:	C, 54.32;	H, 5.10%,
$C_{20}H_{22}O_{11}$ requires:	C, 54.80;	H, 5.06%.

EXAMPLE 2

Synthesis of 3,4,5-trihydroxyacetophenone (X) from IXa

A solution of 6.6 kg of IXa in 15 l of acetic acid containing 5 l of 10% sulphuric acid is agitated for three hours at 80 °C. The solution is diluted with water, extracted with ethyl acetate and the organic phase is concentrated under vacuum to a small volume until there is incipient crystallization. Precipitation is completed by cooling, there being obtained 2.33 kg of X (yield: 92%), m.p. 178-80 °C, M^+ at m/z 168.

Found:	C, 57.00;	H, 4.82%,
$C_8H_6O_4$ requires:	C, 57.11;	H, 4.79%.

EXAMPLE 3

Synthesis of 3,4,5-trihydroxyacetophenone (X) from II

The acid chloride of triacetyl gallic acid (II, 6.7 kg) is subjected to condensation with diethyl malonate (3.6 l) in the presence of magnesium turnings and ethyl alcohol by the procedure described in Example 1. After extraction with ethyl acetate, the organic phase is evaporated to a small volume, diluted with 20 l of

acetic acid containing 6 l of dilute sulphuric acid and kept under agitation at 80°C for three hours. The mixture is diluted with water, extracted with ethyl acetate and the organic phase is evaporated to dryness. The residue, taken up in 5 l of acetic acid, supplies, after filtration and drying, 3.1 kg (yield: 87% of X, identical to the product obtained by the procedure described in Example 2.

EXAMPLE 4

Synthesis of ω -acetoxy-3,4,5-triacetoxyacetophenone (IV)

A suspension of 2.1 kg of X in 9 l of acetic anhydride containing 5 ml of concentrated sulphuric acid is heated for two hours under agitation at 50°C. 0.7 l of bromine is added drop-wise and the mixture is allowed to react under agitation for one hour at room temperature. After dilution with 9 l of glacial acetic acid, 3.6 kg of anhydrous potassium acetate are added, heating is carried out under agitation at 100°C for three hours and the reaction mixture is poured into water/ice. The precipitate is filtered and crystallized from ethyl acetate/cyclohexane. 3.9 kg of IV are obtained (yield: 90%), m.p. 122°C, M^+ at m/z 352.

Found:	C, 54.32;	H, 4.60%,
$C_{15}H_{16}O_9$ requires:	C, 54.54;	H, 4.57%.

EXAMPLE 5

Synthesis of delphinidin chloride (I)

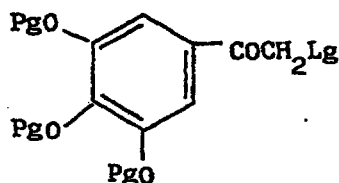
A suspension containing 3.6 kg of phloroglucinaldehyde 2-O-benzoate (V) and 4.6 kg of IV in 50 l of a 2:1 mixture of ethyl acetate and methanol is saturated with gaseous hydrochloric acid under agitation. The mixture is allowed to react to complete dissolution and is kept at rest for 24 hours. The precipitated solid is filtered and suspended under agitation in 40 l of a water-methanol solution containing 2 kg of sodium hydroxide. The reaction mixture is maintained under agitation at 0-4°C for 60 minutes and then poured into 30 l of concentrated hydrochloric acid.

The precipitated solid is filtered, washed with dilute hydrochloric acid and recrystallized from methanol-concentrated hydrochloric acid. 3.5 kg of I are obtained (yield: 80%), having a purity not less than 98% determined by means of HPLC analysis.

Found:	C, 53.26;	H, 3.30;	Cl, 10.51%,
$C_{15}H_{11}ClO_7$ requires:	C, 53.19;	H, 3.27;	Cl, 10.47%.

Claims

1. A process for producing delphinidin which comprises reacting a compound of formula



wherein each Pg represents a hydroxyl protecting group, and Lg represents an acyloxy group with a compound of formula



acetic acid containing 6 l of dilute sulphuric acid and kept under agitation at 80 °C for three hours. The mixture is diluted with water, extracted with ethyl acetate and the organic phase is evaporated to dryness. The residue, taken up in 5 l of acetic acid, supplies, after filtration and drying, 3.1 kg (yield: 87% of X, identical to the product obtained by the procedure described in Example 2.

EXAMPLE 4

Synthesis of ω -acetoxy-3,4,5-triacetoxyacetophenone (IV)

A suspension of 2.1 kg of X in 9 l of acetic anhydride containing 5 ml of concentrated sulphuric acid is heated for two hours under agitation at 50 °C. 0.7 l of bromine is added drop-wise and the mixture is allowed to react under agitation for one hour at room temperature. After dilution with 9 l of glacial acetic acid, 3.6 kg of anhydrous potassium acetate are added, heating is carried out under agitation at 100 °C for three hours and the reaction mixture is poured into water/ice. The precipitate is filtered and crystallized from ethyl acetate/cyclohexane. 3.9 kg of IV are obtained (yield: 90%), m.p. 122 °C, M^+ at m/z 352.

Found:	C, 54.32;	H, 4.60%;
$C_{16}H_{16}O_9$ requires:	C, 54.54;	H, 4.57%.

EXAMPLE 5

Synthesis of delphinidin chloride (I)

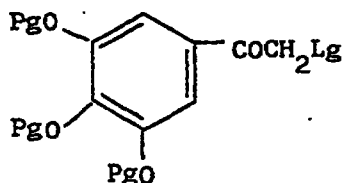
A suspension containing 3.6 kg of phloroglucinaldehyde 2-O-benzoate (V) and 4.6 kg of IV in 50 l of a 2:1 mixture of ethyl acetate and methanol is saturated with gaseous hydrochloric acid under agitation. The mixture is allowed to react to complete dissolution and is kept at rest for 24 hours. The precipitated solid is filtered and suspended under agitation in 40 l of a water-methanol solution containing 2 kg of sodium hydroxide. The reaction mixture is maintained under agitation at 0-4 °C for 60 minutes and then poured into 30 l of concentrated hydrochloric acid.

The precipitated solid is filtered, washed with dilute hydrochloric acid and recrystallized from methanol-concentrated hydrochloric acid. 3.5 kg of I are obtained (yield: 80%), having a purity not less than 98% determined by means of HPLC analysis.

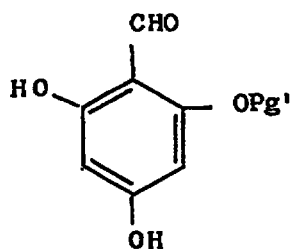
Found:	C, 53.26;	H, 3.30;	Cl, 10.51%;
$C_{15}H_{11}ClO_7$ requires:	C, 53.19;	H, 3.27;	Cl, 10.47%.

Claims

1. A process for producing delphinidin which comprises reacting a compound of formula

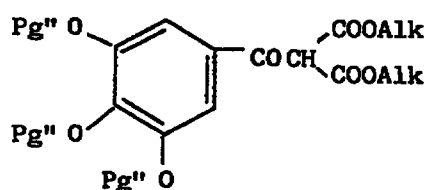


wherein each Pg represents a hydroxyl protecting group, and Lg represents an acyloxy group with a



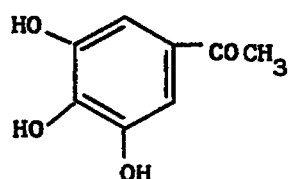
VIII

wherein Pg' represents a hydroxyl protecting group characterised in that the compound of formula VII is produced from an intermediate of formula



IX

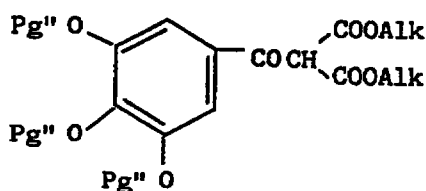
wherein each Pg'' represents a hydroxyl protecting group and each Alk represents lower alkyl, by
(i) subjecting the intermediate of formula IX to hydrolysis and decarboxylation to form 3,4,5-trihydroxyacetophenone of formula



X

(ii) converting the 3,4,5-trihydroxyacetophenone to the compound of formula VII by introduction of the protecting groups Pg and converting the group of formula -COCH₃ to a group of formula -COCH₂Lg.

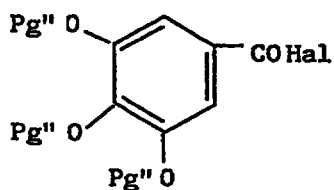
2. A process according to Claim 1 in which the hydrolysis and decarboxylation are carried out in the presence of an acid and at an elevated temperature.
3. A process according to Claim 1 or Claim 2 in which the hydrolysis and decarboxylation are carried out at a temperature of from 50 to 100 °C.
4. A process according to any of Claims 1 to 3 in which the hydrolysis and decarboxylation are carried out in solution in acetic acid in the presence of sulphuric acid.
5. A process according to any of preceding claim wherein the compound of formula (IX)



IX



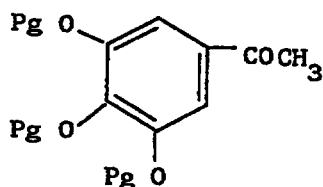
is prepared by reacting a compound of formula



XI

wherein Pg'' represents a hydroxyl protecting group and Hal represents halogen with a source of carbanions derived from a C₁₋₄ di-loweralkyl malonate.

6. A process according to Claim 5 wherein the source of enolate anions comprises ethyl ethoxymagnesium malonate.
7. A process according to Claim 6 wherein the ethyl ethoxymagnesium malonate is produced in situ by reaction between magnesium, ethanol and diethyl malonate in an aprotic solvent.
8. A process according to any preceding claim wherein Pg, Pg' and Pg'' each represents a carboxylic acid acyl group derived from a C₁₋₆ aliphatic carboxylic acid or from a C₆₋₁₀ aromatic carboxylic acid or a radical derived from a sulphonic acid.
9. A process according to any preceding claim wherein Pg and Pg'' each represents acetyl and Pg' is benzoyl.
10. A process according to Claim 1 wherein
 - (i) 3,4,5-trihydroxyacetophenone (X) is esterified to form a compound of formula

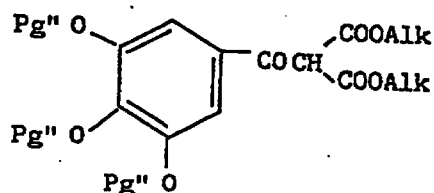


XIV

wherein Pg is a hydroxyl protecting ester group,

(ii) the -COCH₃ group of the compound of formula XIV is converted to a group of the structure -COCH₂Lg wherein Lg is an acyloxy group, by subjecting the compound of formula XIV to ω -bromination to convert said -COCH₃ group to a group of structure -COCH₂Br and reacting the resulting brominated compound with a nucleophilic reagent capable of introducing the group Lg.

11. A compound of formula IX



IX

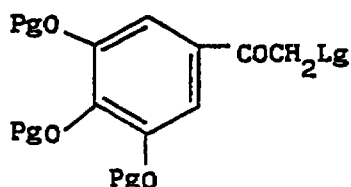
wherein Pg'' represents a carboxylic acid acyl group derived from a C₁₋₆ aliphatic carboxylic acid or



from a C₆₋₁₀ aromatic carboxylic acid or a radical derived from a sulphonic acid and Alk represents C₁₋₄ alkyl.

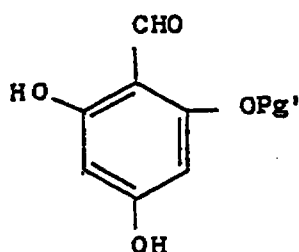
Patentansprüche

1. Verfahren zur Herstellung von Delphinidin, welches die Reaktion einer Verbindung der Formel



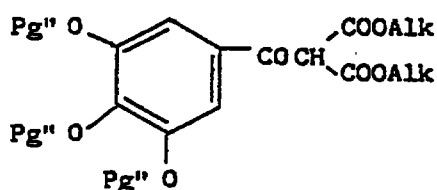
VII

worin Pg jeweils eine Hydroxylschutzgruppe und Lg eine Acyloxygruppe bedeuten mit einer Verbindung der Formel



VIII

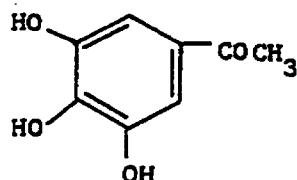
umfaßt, worin Pg' eine Hydroxylschutzgruppe bedeutet, dadurch gekennzeichnet, daß die Verbindung gemäß Formel VII aus einem Zwischenprodukt der Formel



IX

hergestellt wird, worin Pg'' jeweils eine Hydroxylschutzgruppe und Alk jeweils Niedrigalkyl bedeuten, indem man

- (i) das Zwischenprodukt der Formel IX zur Bildung des 3,4,5-Trihydroxyacetophenons der Formel

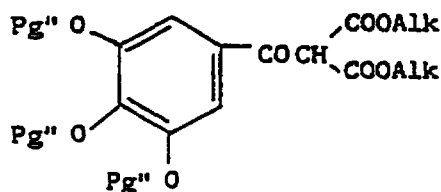


X

- der Hydrolyse und Decarboxylierung unterwirft und
(ii) das 3,4,5-Triacetophenon durch Einführung der Schutzgruppen Pg in die Verbindung der Formel VII überführt und die Gruppe der Formel -COCH₃ in eine Gruppe der Formel -COCH₂Lg umwandelt.

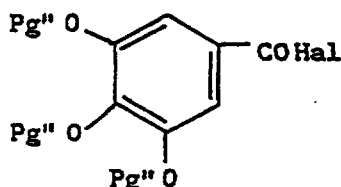


2. Verfahren gemäß Anspruch 1, bei dem Hydrolyse und Decarboxylierung in Anwesenheit einer Säure und bei erhöhter Temperatur durchgeführt werden.
3. Verfahren gemäß einem der Ansprüche 1 oder 2, bei dem die Hydrolyse und Decarboxylierung bei einer Temperatur im Bereich zwischen 50 und 100 °C ausgeführt werden.
4. Verfahren gemäß einem der Ansprüche 1 bis 3, bei dem die Hydrolyse und Decarboxylierung in Lösung in Essigsäure in Anwesenheit von Schwefelsäure vorgenommen werden.
5. Verfahren nach einem der vorstehenden Ansprüche 1 bis 4, bei dem die Verbindung der Formel (IX)



IX

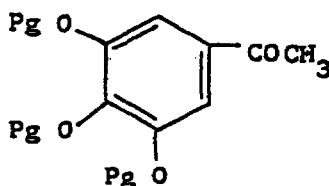
durch die Reaktion einer Verbindung der Formel



XI

mit einer von einem C₁-4-Diniedrigalkylmalonat abgeleiteten Carbanionenquelle hergestellt wird, wobei Pg'' eine Hydroxylschutzgruppe und Hal ein Halogen bedeuten.

6. Verfahren gemäß Anspruch 5, bei dem die Enolatnionenquelle Ethylethoxymagnesiummalonat umfaßt.
7. Verfahren gemäß Anspruch 6, bei dem das Ethylethoxymagnesiummalonat in situ mittels gegenseitiger Reaktion von Magnesium, Ethanol und Diethylmalonat in einem aprotischen Lösungsmittel hergestellt werden.
8. Verfahren gemäß einem der vorstehenden Ansprüche, bei dem Pg, Pg' und Pg'' jeweils eine Acylcarbonsäuregruppe bedeuten, welche von einer aliphatischen C₁-6-Carbonsäuregruppe oder von einer aromatischen C₆-10-Carbonsäure oder einem von einer Sulfonsäure abgeleiteten Radikal hergeleitet sind.
9. Verfahren gemäß einem der vorstehenden Ansprüche, bei dem Pg und Pg'' jeweils Acetyl und Pg' Benzoyl bedeuten.
10. Verfahren gemäß Anspruch 1, bei dem
 - (i) 3,4,5-Trihydroxyacetophenon (X) zur Bildung einer Verbindung der Formel



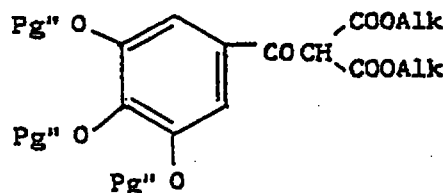
XIV



worin Pg eine Esterhydroxylschutzgruppe bedeutet, verestert wird,

(ii) die $-\text{COCH}_3$ -Gruppe der Verbindung gemäß Formel XIV zu einer Verbindung der Struktur $-\text{COCH}_2\text{Lg}$ umgesetzt wird, worin Lg eine Acyloxygruppe bedeutet, indem man die Verbindung der Formel XIV der ω -Brominierung zur Umwandlung der $-\text{COCH}_3$ -Gruppe in eine Verbindung mit der Struktur $-\text{COCH}_2\text{Br}$ unterzieht und die so erhältliche brominierte Verbindung mit einem nukleophilen Reagenz reagieren läßt, welche die Einführung der Gruppe Lg ermöglicht.

11. Verbindung der Formel IX

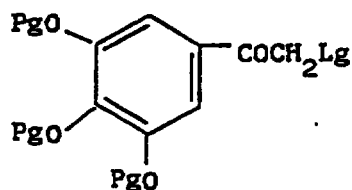


IX

worin Pg'' eine Acylcarbonsäure, welche von einer aliphatischen C_1 - C_6 -Carbonsäure bzw. einer aromatischen C_6 - C_{10} -Carbonsäure abgeleitet wurde, oder ein von der Sulfonsäure abgeleitetes Radikal bedeutet und Alk ein C_1 - C_4 -Alkyl darstellt.

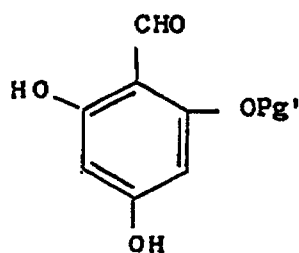
Revendications

1. Procédé de production de delphinidine qui comprend la réaction d'un composé de formule :



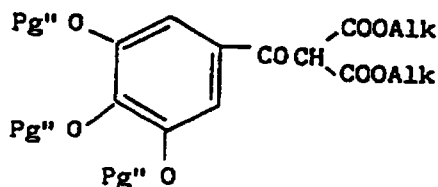
VII

dans lequel chaque Pg représente un groupe hydroxyl protecteur, et Lg représente un groupe acyloxy, avec un composé de formule :



VIII

dans lequel Pg' représente un groupe hydroxyle protecteur, caractérisé en ce que le composé de formule (VII) est produit à partir d'un intermédiaire de formule :

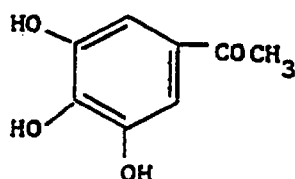


IX



dans lequel chaque Pg'' représente un groupe hydroxyle protecteur et chaque Alk représente un groupe alkyle inférieur,

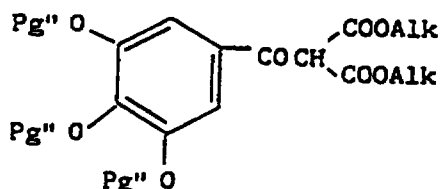
(i) en soumettant l'intermédiaire de formule (IX) à une hydrolyse et à une décarboxylation pour former la 3,4,5-trihydroxyacétophénone de formule :



X

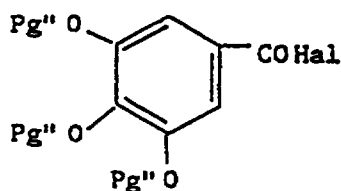
(ii) en convertissant la 3,4,5-trihydroxyacétophénone en composé de formule (VII) par l'introduction des groupes protecteurs Pg et en convertissant le groupe de formule -CO CH₃ en un groupe de formule -COCH₂Lg.

2. Procédé suivant la revendication 1 dans lequel l'hydrolyse et la décarboxylation sont effectuées en présence d'un acide et à une température élevée.
3. Procédé suivant la revendication 1 ou suivant la revendication 2, dans lequel l'hydrolyse et la décarboxylation sont effectuées à une température comprise entre 50 et 100 °C.
4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel l'hydrolyse et la décarboxylation sont effectuées en solution dans l'acide acétique, en présence d'acide sulfurique.
5. Procédé suivant l'une quelconque des revendications précédentes dans lequel le composé de formule (IX)



IX

est préparé en faisant réagir un composé de formule



XI

dans lequel Pg'' représente un groupe hydroxyle protecteur et Hal représente un halogène, avec une source de carbanions dérivés d'un malonate de dialkyle C₁₋₄ inférieur.

6. Procédé suivant la revendication 5, dans lequel la source d'anions énoles comprend le malonate d'éthyle éthoxymagnésium.
7. Procédé suivant la revendication 6, dans lequel le malonate d'éthyle éthoxymagnésium est produit in situ, par réaction entre le magnésium, l'éthanol et le malonate de diéthyle, dans un solvant aprotique.

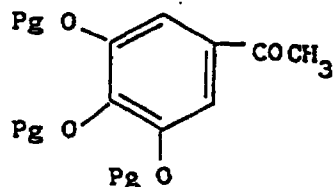


8. Procédé suivant l'une quelconque des revendications précédentes, dans lequel Pg, Pg', et Pg'' représentent chacun, un groupe acyle d'acide carboxylique dérivé d'un acide carboxylique aliphatique C₁₋₆, ou d'un acide carboxylique aromatique C₆₋₁₀, ou d'un radical dérivé d'un acide sulfonique.

9. Procédé suivant l'une quelconque des revendications précédentes, dans lequel Pg, Pg'' représentent chacun un groupe acétyle, Pg' représente un groupe benzoyle.

10. Procédé suivant la revendication 1, dans lequel

(i) la 3,4,5-trihydroxyacétophénone (X) est estérifiée pour donner un composé de formule :

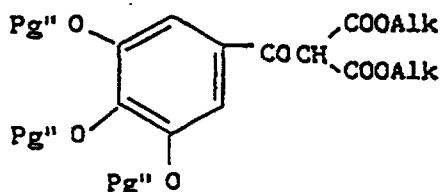


XIV

dans lequel Pg est un groupe ester, hydroxyle protecteur.

(ii) le groupe -COCH₃ du composé de formule (XIV) est converti en un groupe de structure -COCH₂Lg dans lequel Lg est un groupe acyloxy, en soumettant le composé de formule (XIV) à une ω-bromuration pour convertir ledit groupe -COCH₃ en un groupe de structure -COCH₂Br et en faisant réagir le composé bromé obtenu, avec un agent nucléophile capable d'introduire le groupe Lg.

11. Composé de formule (IX)



IX

dans lequel Pg'' représente un groupe acyle d'acide carboxylique dérivé d'un acide carboxylique aliphatique C₆₋₁₀, ou d'un radical dérivé d'un acide sulfonique, et Alk représente un groupe alkyle C₁₋₄.