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**DSM Fine Chemicals Austria Nfg GmbH & Co**  
**KG, 4021 Linz (AT)**(72) Feltaláló(k):  
**STANEK, Michael, A-4020 Linz (AT)**  
**ESSL, Stefan, 79589 Binzen (DE)**  
**KNOPP, Monika, CH-4310 Rheinfelden (CH)**  
**KÜBEL, Erwin, A-4020 Linz (AT)**(74) Képviselő:  
**dr. Fehérvári Flóra, DANUBIA Szabadalmi és**  
**Jogi Iroda Kft., Budapest**(54) **Javított eljárás 9-cisz-retinoészav előállítására**

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

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(54) **IMPROVED METHOD OF PRODUCTION OF 9-CIS-RETINOIC ACID**

VERBESSERTES VERFAHREN ZUR HERSTELLUNG VON 9-CIS-RETINSÄURE

PROCÉDÉ AMÉLIORÉ POUR LA PRODUCTION D'ACIDE 9-CIS-RÉTINOÏQUE

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(73) Proprietor: **DSM Fine Chemicals Austria Nfg  
GmbH & Co KG  
4021 Linz (AT)**

(72) Inventors:  
• **STANEK, Michael  
A-4020 Linz (AT)**

• **ESSL, Stefan  
79589 Binzen (DE)**  
• **KNOPP, Monika  
CH-4310 Rheinfelden (CH)**  
• **KÜBEL, Erwin  
A-4020 Linz (AT)**

(74) Representative: **Duffy, James Edwin Marsh et al  
DSM Intellectual Property  
P.O. Box 4  
6100 AA Echt (NL)**

(56) References cited:  
**EP-A- 0 659 739 WO-A-2004/089887**

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## Description

**[0001]** The present invention relates to an improved method of production of 9-cis-retinoic acid.

**[0002]** As is known for example from Nature 355 (1992), pages 359-361, 9-cis-retinoic acid is a physiologically important compound and can be used in a variety of applications, such as for the treatment of various skin diseases (e.g. WO 99/09969).

**[0003]** A method is known from EP 0 659 739 A1 for the production of 9-cis-retinoic acid (9-(Z)-RA) in which a  $\beta$ -formylcrotonic acid alkyl ester is reacted with a  $C_{15}$ -triarylphosphonium salt by the Wittig reaction in the presence of a base to the corresponding 9-(Z)-retinoic acid ester, which is then saponified with a base to the desired acid. In this process, the mother liquor that arises in the commercial production of  $C_{15}$ -triarylphosphonium salts is used as  $C_{15}$ -triarylphosphonium salt, with the 9-(Z)- $C_{15}$ -triarylphosphonium salt fraction being enriched, but not isolated, by treatment with isopropanol while hot, cooling and separation of the crystallizing all-(E)- $C_{15}$ -triarylphosphonium salt.

**[0004]** According to WO 2004/089887, a drawback of this method is that it is a two-stage process, in which in addition a change of solvent is necessary for the saponification.

**[0005]** As an improvement, it is proposed to react an alkali-metal salt of 3-methyl-4-oxocrotonic acid with the isolated (Z)-isomer of a  $C_{15}$ -triarylphosphonium salt in the presence of a base, by which the desired 9-(Z)-retinoic acid is obtained directly.

**[0006]** However, both methods have the disadvantage of low yield of the desired acid. (EP 0 659 739: ~ 25%; WO 2004/089887: only about 16%).

**[0007]** The task of the present invention was therefore to find an improved method of production of 9-(Z)-retinoic acid, which supplies the desired acid at much higher yields.

**[0008]** Accordingly, the present invention relates to an improved method of production of 9-(Z)-retinoic acid, which is characterized in that

a) a  $\beta$ -formylcrotonic acid- $C_1$ - $C_{10}$  linear, branched or cyclic alkyl or phenyl ester is reacted by the Wittig reaction with a 9-(Z)- $C_{15}$ -triarylphosphonium salt in isolated form in the presence of a base to the corresponding 9-(Z)-retinoic acid ester, and

b) after the end of the Wittig reaction the reaction mixture is then saponified with a base to the corresponding 9-(Z)-retinoic acid carboxylate and then, following protonation with an acid, the desired 9-(Z)-retinoic acid is obtained.

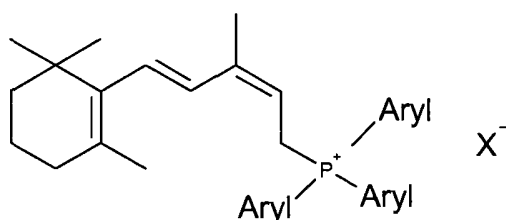
**[0009]** According to the present invention, in the first step  $\beta$ -formylcrotonic acid - $C_1$ - $C_{10}$  linear, branched or cyclic alkyl or phenyl ester is reacted by the Wittig reaction with a 9-(Z)- $C_{15}$ -triarylphosphonium salt in isolated form in the presence of a base to the corresponding 9-(Z)-retinoic acid ester.

**[0010]**  $\beta$ -Formylcrotonic acid methyl- $C_1$ - $C_{10}$  linear, branched or cyclic alkyl or phenyl esters can be prepared for example according to EP 0 421 271.

**[0011]** Linear, branched or cyclic alkyl denotes residues, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec. butyl, tert. butyl, hexyl or cyclohexyl.

**[0012]** Preferably the  $\beta$ -formylcrotonic acid methyl or ethyl ester is used as educt.

**[0013]** 9-(Z)- $C_{15}$ -Triarylphosphonium salts are compounds of formula (I)



in which aryl represents an optionally substituted  $C_6$ - $C_{10}$ -aryl residue, such as phenyl, naphthyl, tolyl or xylyl and X represents a halogen, such as chlorine, bromine or iodine. Preferably aryl denotes a phenyl residue and X denotes chlorine or bromine.

**[0014]** According to the present invention, the 9-(Z)- $C_{15}$ -triarylphosphonium salt is used in isolated form.

**[0015]** A mother liquor that arises in the industrial production of  $C_{15}$ -triarylphosphonium salts is used for this. Thus, for example in the production of the  $C_{15}$ -triarylphosphonium salt required for industrial vitamin-A syntheses,  $\beta$ -carotene syntheses and canthaxanthin syntheses, and for the production of other vitamin-A derivatives, such as retinal and retinoic acid, (see e.g. Angew. Chem. 77 (1965), 277-360) after separating the valuable product a mother liquor is obtained that contains the 9-(Z) isomer as well as all-(E)- $C_{15}$ -triphenylphosphonium salt.

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[0016] For the method according to the invention the 9-(Z) isomer is first enriched, and then isolated.

[0017] For this, preferably

- a) the mother liquor is extracted with methylene chloride, then
- b) the organic phase is re-extracted with water and
- c) the methylene chloride phase is separated from the aqueous phase, then
- d) 50-70% methylene chloride is distilled off, and
- e) ethyl acetate and seed crystals are added to the concentrated methylene chloride solution at 15-40°C, preferably at 20-30°C, then
- f) the solution is stirred at 15-40°C, preferably at 20-30°C, and the enriched 9-(Z) isomer precipitates and
- g) then the enriched 9-(Z)-C<sub>15</sub>-triarylphosphonium salt is separated by filtration while moist, and is washed with ethyl acetate.
- h) Next, the 9-(Z) isomer is dissolved in methylene chloride and this solution is added dropwise at 20-40°C, preferably at 15-30°C, to a defined amount of ethyl acetate, then
- i) the resultant suspension is stirred and
- j) finally the enriched 9-(Z)-C<sub>15</sub>-triarylphosphonium salt is separated by filtration, washed with ethyl acetate and then dried.

[0018] With this method of enrichment, which is improved relative to the state of the art, a 9-(Z)-C<sub>15</sub>-triarylphosphonium salt in isolated form is obtained with a ratio of Z fraction to E fraction of 98:2.

[0019] If necessary, steps h - j can be omitted, obtaining a higher yield of 9-(Z)-C<sub>15</sub>-triarylphosphonium salt, but of somewhat lower purity (with a ratio of Z fraction to E fraction of 96:4). This quality is, however, also sufficient for production of 9-(Z)-retinoic acid according to the invention.

[0020] The Wittig reaction of the β-formyl-crotonic acid ester (C<sub>5</sub>- ester) with the 9-(Z)-C<sub>15</sub>-triarylphosphonium salt in isolated form is then carried out in a solvent mixture of a C<sub>1</sub>-C<sub>4</sub> alcohol, such as methanol, ethanol, etc. and a non-polar solvent from the group methylene chloride, hexane or toluene.

[0021] A dichloromethane-alcohol mixture is preferably used.

[0022] The molar ratio of C<sub>15</sub> salt to C<sub>5</sub> ester is 1:1 to 1:5, preferably 1:1 to 1:2, especially preferably 1:1.1.

[0023] The reaction temperatures are from -40 to +40°C, preferably from -30 to -20°C, depending on the composition of the solvent mixture.

[0024] The base used in the method according to the invention is an alkali-metal or alkaline-earth C<sub>1</sub>-C<sub>4</sub> alcoholate, carbonate, hydroxide, hydride or amide. Li-, Na- or K- alcoholates, carbonates, hydroxides, hydrides and amides are preferred, and sodium methylate, ethylate or propylate, sodium hydroxide and potassium carbonate are especially preferred.

[0025] It is possible to start either with both starting compounds in the solvent mixture, then adding the base, or it is also possible to add one of the educts, either the C<sub>15</sub> salt or the β-formyl-crotonic acid ester.

[0026] Preferably only the base is added.

[0027] The Wittig reaction leads to the retinoic acid ester. At the end of the Wittig reaction the mixture is heated to room temperature and saponified with an aqueous alkali-metal or alkaline-earth hydroxide solution. For this, the reaction mixture is heated further to 30 to 100°C, preferably to 50-80°C and all low-boiling substances are distilled off. Then by adding an acid, such as HCl, H<sub>2</sub>SO<sub>4</sub>, acetic acid, phosphoric acid, etc., to the cooled alkaline reaction mixture, the 9-(Z)-retinoic acid is released and crystallizes out.

[0028] The 9-(Z)-retinoic acid thus obtained can then be purified by extraction, optionally in combination with recrystallization. The preferred solvents for extraction are water and dichloromethane. Recrystallization is preferably carried out in C<sub>1</sub>-C<sub>4</sub> alcohols or C<sub>1</sub>-C<sub>4</sub> alcohol mixtures, preferably ethanol.

[0029] Using the method according to the invention, 9-(Z)-retinoic acid is obtained at much higher yields compared with the state of the art, of more than 45% of the theoretical, and also at higher purities of > 98%.

### Example 1: Enrichment of the C<sub>15</sub> salt according to the invention

[0030] 300 g of mother liquor (containing approx. 30% of valuable product) from the production of C<sub>15</sub>-triphenylphosphonium chloride was mixed with 240 ml dichloromethane and stirred for 30 min. Then the phases were separated and the organic phase was washed with 450 ml water. 5g of table salt was added to the aqueous phase. The phases were separated and the aqueous phase was extracted again with 150 ml dichloromethane. The combined organic phases were concentrated at 40°C. Approx. 240 ml dichloromethane was distilled off, so that 150 ml dichloromethane remained in the flask. The mixture was cooled to 25°C, 1500 ml ethyl acetate and a spatula tip of seed crystals were added, and filtration was carried out after 60 min. The precipitate was washed with 150 ml ethyl acetate.

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Recrystallization:

[0031] The raw product was dissolved in 150 ml dichloromethane and then added in the space of 30 min at 30°C to 1500 ml ethyl acetate while stirring. After stirring for a further 30 min, the 9-(Z)-C<sub>15</sub>-triphenylphosphonium chloride was filtered off and washed twice with 150 ml ethyl acetate each time, and dried to constant weight. 9-(Z)-C<sub>15</sub>-Triphenylphosphonium chloride was obtained at a yield of 69 g and a purity of > 97% (Z). The yield was 66.9%

### Example 2: Production of 9-(Z)-retinoic acid

a) Wittig reaction:

[0032] First, a double-jacket reactor was gassed with nitrogen for at least 15 min.

[0033] Then 51.13 g C<sub>15</sub>-vinyl salt (content of cis + trans C<sub>15</sub> vinyl salt > 98.5%) and 14.24 g C<sub>5</sub> ester (w = 0.99) were added with a disposable syringe. Residues of substance in the funnel were rinsed with 276.85 g (350 ml) methanol (w = 1.0) into the reactor and the slightly yellowish solution was cooled under a gentle stream of nitrogen to an internal temperature of -7.5°C.

[0034] Then 50.42 g (52.0 ml) sodium methylate was fed in at -7.5°C internal temperature in the space of 60 minutes.

[0035] Then 157.80 g (200.0 ml) of ethanol (w = 1.0) was added. b) Saponification / hydrolysis

[0036] 48.52 g (37.14 ml) NaOH (28%) was fed in at 20°C and the orange suspension was heated to reflux. After distillation of methanol/ethanol the suspension was cooled to room temperature and 265.00 g (200 ml) methylene chloride, 299.40 g (300 ml) water and 71.00 g (67.7 ml) acetic acid were added.

c) Extraction

[0037] 662.5 g (500 ml) methylene chloride was added to the above solution and the organic phase was extracted twice, each time with 199.6 g (200 ml) water WBI (w = 1.0).

[0038] Then the combined organic phases were concentrated in the rotary evaporator at 35°C, obtaining raw retinoic acid.

d) Recrystallization

[0039] The raw retinoic acid thus obtained was suspended in 235.5 g (300 ml) isopropanol (w = 1.0) and refluxed.

[0040] Then it was crystallized and the crystals were filtered off. The crystals were washed with approx. 39.55 g (50 ml) isopropanol -10°C (w = 1.0) and then dried at high vacuum.

Yields

[0041]

Products	Quantity	Content (cis-RTA)	Quantity 100%	Molar mass	Yield (trans) based on C-15 vinyl salt used
	[g]	[%]	[g]	[g/mol]	[% of theor.]
Retinoic acid	Approx. 14g	Approx. 98	13.7	300.44	Approx. 46

### Example 3: Comparative test according to BASF patent

[0042] The yields stated in the BASF patent (EP0659739) were verified in the laboratory (Table).

### Example 4: Comparative test according to Roche patent

[0043] The yields stated in the Roche patent (WO2004/089887) were verified in the laboratory (Table).

	BASF	Roche	DSM
Yield Vinyl salt	46%	31%	67%
Content:	65.8% Z	93.6% Z	98% Z

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(continued)

	BASF	Roche	DSM
	19.0% E	5% E	2% E
Yield Retinoic acid incl. recrystallization	25%	15.5%	40-45%
Content:	99.5%	??%	> 99.5%

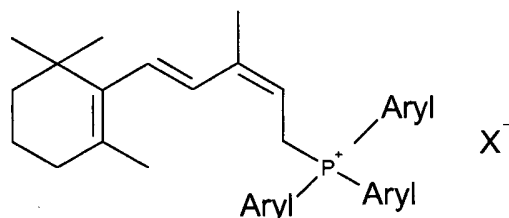
Claims

1. Improved method of production of 9-(Z)-retinoic acid, **characterized in that**

a) a  $\beta$ -formyl-crotonic acid -C<sub>1</sub>-C<sub>10</sub> linear, branched or cyclic alkyl or phenyl ester is reacted by the Wittig reaction with a 9-(Z)-C<sub>15</sub>-triarylphosphonium salt in isolated form in the presence of a base to the corresponding 9-(Z)-retinoic acid ester, and

b) after the end of the Wittig reaction the reaction mixture is then saponified with a base to the corresponding 9-(Z)-retinoic acid carboxylate and then, following protonation with an acid, the desired 9-(Z)-retinoic acid is obtained.

2. Method according to Claim 1, **characterized in that** a compound of formula (I)



in which aryl represents an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl residue and X represents a halogen, is used as the 9-(Z)-C<sub>15</sub>-triarylphosphonium salt.

3. Method according to Claim 1, **characterized in that** the reaction in step a) takes place in a solvent mixture of a C<sub>1</sub>-C<sub>4</sub> alcohol and a non-polar solvent from the group methylene chloride, hexane and toluene.

4. Method according to Claim 1, **characterized in that** the reaction in step a) is carried out at a reaction temperature from -40°C to +40°C.

5. Method according to Claim 1, **characterized in that** the reaction in step a) takes place in the presence of a base from the group comprising the alkali-metal or alkaline-earth C<sub>1</sub>-C<sub>4</sub> alcoholates, carbonates, hydroxides, hydrides or amides.

6. Method according to Claim 1, **characterized in that** the 9-(Z)-retinoic acid ester obtained is not isolated from the reaction mixture, but after the end of the Wittig reaction the reaction mixture is if necessary heated to room temperature and is saponified in step b) with an aqueous alkali-metal or alkaline-earth hydroxide solution as base.

7. Method according to one of Claims 1 to 6, **characterized in that** in step b), after adding the base, the low-boiling substances are distilled off and then, by adding an acid to the cooled alkaline reaction mixture, the desired 9-(Z)-retinoic acid is released and crystallized.

8. Method according to one of claims 1-7, **characterized in that** the 9-(Z)-C<sub>15</sub>-triarylphosphonium salt is obtained by enrichment and isolation of 9-(Z)-C<sub>15</sub>-triarylphosphonium salt from a mother liquor that arises in the production of vitamin A and its derivatives,  $\beta$ -carotene or canthaxanthin, wherein

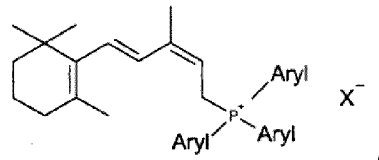
a) the mother liquor is extracted with methylene chloride, then

b) the organic phase is re-extracted with water and

- c) the methylene chloride phase is separated from the aqueous phase, then  
 d) 50-70% methylene chloride is distilled off, and  
 e) ethyl acetate and seed crystals are added to the concentrated methylene chloride solution at 15-40°C, then  
 f) the solution is stirred at 15-40°C, and the enriched 9-(Z) isomer precipitates and  
 5 g) then the enriched 9-(Z)-C<sub>15</sub>-triarylphosphonium salt is separated by filtration while moist, and is washed with ethyl acetate.  
 h) optionally, next the 9-(Z) isomer is dissolved in methylene chloride and this solution is added dropwise at 20-40°C to a defined amount of ethyl acetate, then  
 i) the resultant suspension is stirred and  
 10 j) finally the enriched 9-(Z)-C<sub>15</sub>-triarylphosphonium salt is separated by filtration, washed with ethyl acetate and then dried.

Patentansprüche

- 15 1. Verbessertes Verfahren zur Herstellung von 9-(Z)-Retinsäure, **dadurch gekennzeichnet, dass** man a) einen mit linearem, verzweigtem oder cyclischem C<sub>1</sub>-C<sub>10</sub>-Alkyl oder mit Phenyl gebildeten Ester der β-Formylcrotonsäure in einer Wittig-Reaktion mit einem 9-(Z)-C<sub>15</sub>-Triarylphosphoniumsalz in isolierter Form in Gegenwart einer Base zum entsprechenden 9-(Z)-Retinsäureester umsetzt und b) nach dem Ende der Wittig-Reaktion den Reaktionsansatz  
 20 dann mit einer Base zum entsprechenden 9-(Z)-Retinsäurecarboxylat verseift und anschließend nach Protonierung mit einer Säure die gewünschte 9-(Z)-Retinsäure erhält.
2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** eine Verbindung der Formel (I)



in der Aryl einen gegebenenfalls substituierten C<sub>6</sub>-C<sub>10</sub>-Arylrest und X ein Halogen repräsentiert, als 9-(Z)-C<sub>15</sub>-Triarylphosphoniumsalz verwendet wird.

- 35 3. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** die Umsetzung in Schritt a) in einem Lösungsmittelgemisch aus einem C<sub>1</sub>-C<sub>4</sub>-Alkohol und einem unpolaren Lösungsmittel aus der Gruppe Methylenchlorid, Hexan und Toluol erfolgt.
- 40 4. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** die Umsetzung in Schritt a) bei einer Reaktionstemperatur von -40°C bis +40°C durchgeführt wird.
- 45 5. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** die Umsetzung in Schritt a) in Gegenwart einer Base aus der die Alkalimetall- oder Erdalkali-C<sub>1</sub>-C<sub>4</sub>-alkoholate, -carbonate, -hydroxide, -hydride oder -amide umfassenden Gruppe erfolgt.
- 50 6. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** der erhaltene 9-(Z)-Retinsäureester nicht aus dem Reaktionsansatz isoliert wird, sondern dass nach dem Ende der Wittig-Reaktion der Reaktionsansatz, falls notwendig, auf Raumtemperatur erwärmt und in Schritt b) mit einer wässrigen Alkalimetall- oder Erdalkalihydroxidlösung als Base verseift wird.
- 55 7. Verfahren nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, dass** in Schritt b) nach Zugabe der Base die niedrig siedenden Stoffe abdestilliert werden und anschließend durch Versetzen des abgekühlten alkalischen Reaktionsansatzes mit einer Säure die gewünschte 9-(Z)-Retinsäure freigesetzt und kristallisiert wird.
8. Verfahren nach einem der Ansprüche 1-7, **dadurch gekennzeichnet, dass** das 9-(Z)-C<sub>15</sub>-Triarylphosphoniumsalz durch Anreicherung und Isolierung von 9-(Z)-C<sub>15</sub>-Triarylphosphoniumsalz aus einer Mutterlauge, die bei der Herstellung von Vitamin A und seinen Derivaten, β-Carotin oder Canthaxanthin entsteht, erhalten wird, wobei

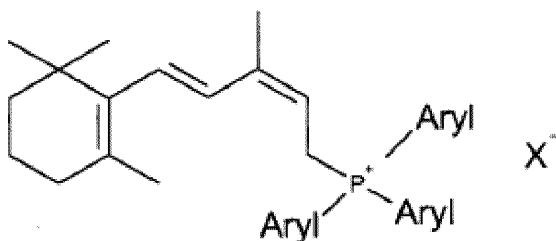
- a) die Mutterlauge mit Methylenchlorid extrahiert wird, danach  
 b) die organische Phase mit Wasser rückextrahiert wird und  
 c) die Methylenchloridphase von der wässrigen Phase getrennt wird, danach  
 d) 50-70% Methylenchlorid abdestilliert werden und  
 e) die konzentrierte Methylenchloridlösung bei 15-40°C mit Essigsäureethylester und Impfkristallen versetzt wird, danach  
 f) die Lösung bei 15-40°C gerührt wird, wobei das angereicherte 9-(Z)-Isomer ausfällt, und  
 g) danach das angereicherte 9-(Z)-C<sub>15</sub>-Triaryl-phosphoniumsalz im feuchten Zustand durch Filtration abgetrennt und mit Essigsäureethylester gewaschen wird,  
 h) gegebenenfalls als Nächstes das 9-(Z)-Isomer in Methylenchlorid gelöst und diese Lösung bei 20-40°C in eine vorgegebene Menge an Essigsäureethylester getropft wird, danach  
 i) die erhaltene Suspension gerührt wird und  
 j) schließlich das angereicherte 9-(Z)-C<sub>15</sub>-Triaryl-phosphoniumsalz durch Filtration abgetrennt, mit Essigsäureethylester gewaschen und danach getrocknet wird.

### Revendications

1. Procédé amélioré de production d'acide 9-(Z)-rétinoïque, **caractérisée en ce que**

- a) un ester d'alkyle linéaire, ramifié ou cyclique en C<sub>1</sub>-C<sub>10</sub> ou de phényle d'acide β-formyl-crotonique réagit par la réaction de Wittig avec un sel de 9-(Z)-C<sub>15</sub>-triarylphosphonium sous forme isolée en présence d'une base pour former l'ester d'acide 9-(Z)-rétinoïque correspondant, et  
 b) après la fin de la réaction de Wittig, le mélange de réaction est ensuite saponifié avec une base pour obtenir le carboxylate d'acide 9-(Z)-rétinoïque correspondant et ensuite, après protonation avec un acide, l'acide 9-(Z)-rétinoïque souhaitée est obtenu.

2. Procédé selon la revendication 1, **caractérisé en ce qu'**un composé de formule (I)



dans lequel Aryl représente un résidu aryle en C<sub>6</sub>-C<sub>10</sub> facultativement substitué et X représente un halogène, est utilisé en tant que sel de 9-(Z)-C<sub>15</sub>-triarylphosphonium.

3. Procédé selon la revendication 1, **caractérisé en ce que** la réaction dans l'étape a) est conduite dans un mélange de solvants d'un alcool en C<sub>1</sub>-C<sub>4</sub> et un solvant non polaire dans le groupe du dichlorométhane, de l'hexane et du toluène.  
 4. Procédé selon la revendication 1, **caractérisé en ce que** la réaction dans l'étape a) est conduite à une température de réaction de -40 °C à +40 °C.  
 5. Procédé selon la revendication 1, **caractérisé en ce que** la réaction dans l'étape a) est conduite en présence d'une base dans le groupe comprenant les alcoolates en C<sub>1</sub>-C<sub>4</sub>, carbonates, hydroxydes, hydrures ou amides de métal alcalin ou alcalino-terreux.  
 6. Procédé selon la revendication 1, **caractérisé en ce que** l'ester d'acide 9-(Z)-rétinoïque obtenu n'est pas isolé à partir du mélange de réaction, mais après la fin de la réaction de Wittig, si nécessaire, le mélange de réaction est chauffé à température ambiante et est saponifié dans l'étape b) avec une solution d'hydroxyde de métal alcalin ou alcalino-terreux en tant que base.

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7. Procédé selon une de revendications 1 à 6, **caractérisé en ce que** dans l'étape b), après l'ajout de la base, les substances à bas point d'ébullition sont distillées et ensuite, par ajout d'un acide au mélange de réaction alcalin refroidi, l'acide 9-(Z)-rétinoïque souhaité est libéré et cristallisé.
- 5 8. Procédé selon une des revendications 1 à 7, **caractérisé en ce que** le sel de 9-(Z)-C<sub>15</sub>-triarylphosphonium est obtenu par enrichissement et isolement de sel de 9-(Z)-C<sub>15</sub>-triarylphosphonium à partir d'une liqueur mère qui est obtenue dans la production de vitamine A et ses dérivés, β-carotène ou canthaxanthine, dans lequel
- 10 a) la liqueur mère est extraite avec du dichlorométhane, ensuite  
b) la phase organique est ré-extraite avec de l'eau et  
c) la phase de dichlorométhane est séparée de la phase aqueuse, puis  
d) 50 - 70 % du dichlorométhane est distillée, et  
e) de l'acétate d'éthyle et des cristaux de Germain sont ajoutés à la solution concentrée de dichlorométhane à 15 - 40 °C, puis
- 15 f) la solution est agitée à 15 - 40 °C, et l'isomère 9-(Z) enrichi précipite et  
g) ensuite, le sel de 9-(Z)-C<sub>15</sub>-triarylphosphonium enrichi est séparé par filtration à l'état humide, et est lavé avec de l'acétate d'éthyle  
h) facultativement, ensuite, l'isomère 9-(Z) est dissous dans du dichlorométhane et cette solution est ajoutée goutte-à-goutte à 20 - 40 °C à une quantité définie d'acétate d'éthyle, puis
- 20 i) la suspension résultante est agitée et  
j) finalement, le sel de 9-(Z)-C<sub>15</sub>-triarylphosphonium enrichi est séparé par filtration, lavé avec de l'acétate d'éthyle et ensuite séché.
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**REFERENCES CITED IN THE DESCRIPTION**

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## Javított eljárás 9-cisz-retinoésvav előállítására

## Szabadalmi igénypontok

1. Javított eljárás 9-(Z)-retinoésvav előállítására, azzal jellemezve, hogy

a)  $\beta$ -formil-krotonsvav-(C<sub>7</sub>-C<sub>10</sub> egyenes láncú, elágazó vagy gyűrűs alkil)- vagy fenil-észtert Wittig reakcióval reagáltatunk 9-(Z)-C<sub>15</sub>-trialkilfoszfónium-sóval, izolált formában egy bázis jelenlétében, így kapjuk megfelelő 9-(Z)-retinoésvav-észtert, és

b) a Wittig reakció befejeződése után a reakciókeveréket egy bázissal elszappanosítva a megfelelő 9-(Z)-retinoésvav-karboxilátot kapjuk, majd egy savval protonáljuk, így kapjuk az előállítani kívánt 9-(Z)-retinoésvavat.

2. Az 1. igénypont szerinti eljárás, azzal jellemezve, hogy egy (I) képletű vegyületet,



amelyben aril jelentése adott esetben szubsztituált C<sub>6</sub>-C<sub>10</sub> aril-maradék és X jelentése halogénatom, használunk 9-(Z)-C<sub>15</sub>-trialkilfoszfónium-sóként.

3. Az 1. igénypont szerinti eljárás, azzal jellemezve, hogy az a) lépésben a reakciót egy C<sub>1</sub>-C<sub>4</sub> alkohol és egy, metilén-klorid, hexán és toluol csoportjából kiválasztott nem-poláros oldószer oldószerkeverékében végezzük.

4. Az 1. igénypont szerinti eljárás, azzal jellemezve, hogy az a) lépésben a reakciót -40°C – +40°C reakcióhőmérsékleten végezzük.

5. Az 1. igénypont szerinti eljárás, azzal jellemezve, hogy az a) lépésben a reakció egy, alkálifém- vagy alkáliföldfém-C<sub>1</sub>-C<sub>4</sub> alkoholátok, -karbonátok, -hidroxidok, -hidridek vagy -amidok csoportjából kiválasztott bázis jelenlétében megy végbe.

6. Az 1. igénypont szerinti eljárás, azzal jellemezve, hogy a kapott 9-(Z)-retinoésvav-észtert nem izoláljuk a reakciókeverékből, hanem a Wittig reakció befejeződése után a reakciókeveréket, ha szükséges, szobahőmérsékletre melegítjük és a b) lépésben vízes alkálifém- vagy alkáliföldfém-hidroxid-oldattal mint bázissal elszappanosítjuk.

7. Az 1-6. igénypontok bármelyike szerinti eljárás, azzal jellemezve, hogy a b) lépésben a bázis hozzáadása után az alacsony forráspontú anyagokat ledesztilláljuk, majd a lehűtött lúgos reakciókeverékhez egy savat adva az előállítani kívánt 9-(Z)-retinoésvavat felszabadítjuk és kristályosítjuk.

8. Az 1-7. igénypontok bármelyike szerinti eljárás, azzal jellemezve, hogy a 9-(Z)-C<sub>15</sub>-triarilfoszfónium-sót úgy állítjuk elő, hogy a 9-(Z)-C<sub>15</sub>-triarilfoszfónium-sót dúsítjuk és izoláljuk az A vitamin és származékai, a  $\beta$ -karotin vagy a kantaxantin előállításakor keletkező anyalúgból, ahol

- a) az anyaglúgot metilén-kloriddal extraháljuk, majd
  - b) a szerves fázist vízzel vissza-extraháljuk, és
  - c) a metilén-kloridos fázist a vízes fázistól elválasztjuk, majd
  - d) 50-70% metilén-kloridot ledesztülálunk, és
  - e) etil-acetátot és oltókristályokat adunk 15-40°C-on a koncentrált metilén-klorid-oldathoz, majd
  - f) az oldatot 15-40°C-on keverjük és a dúsított 9-(Z) izomert kicsapjuk, és
  - g) ezután a dúsított 9-(Z)-C<sub>15</sub>-triarilfoszfónium-sót szűrővel elválasztjuk, közben megnedvestjük, és etil-acetáttal mossuk.
- b) adott esetben ezután a 9-(Z) izomert metilén-kloridban oldjuk, és ezt az oldatot cseppenként 20-40°C-on meghatározott mennyiségű etil-acetáthoz adjuk, majd
- i) a kapott szuszpenziót összekeverjük, és
  - j) végül a dúsított 9-(Z)-C<sub>15</sub>-triarilfoszfónium-sót szűrővel elválasztjuk, etil-acetáttal mossuk, majd megszáritjuk.