(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 October 2020 (22.10.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/212166 A1

(51) International Patent Classification:
*C07C 403/12* (2006.01)

(21) International Application Number:
PCT/EP2020/059482

(22) International Filing Date:
03 April 2020 (03.04.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
19169208.6 15 April 2019 (15.04.2019) EP

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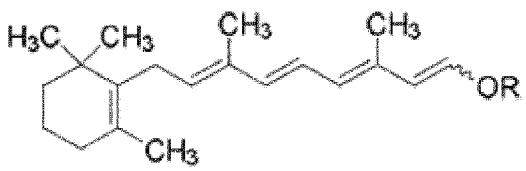
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

**Published:**
— *with international search report (Art. 21(3))*

(54) Title: NOVEL ENOL-ACETATES(II)




(I)

(57) Abstract: The present invention relates to new specific enol esters of formula (I) as well as to a process for their production by acylation of the corresponding dihydroretinal analogue. In formula (I) R is -COR' where R' is a $C_1$-$C_{16}$ alkyl group.

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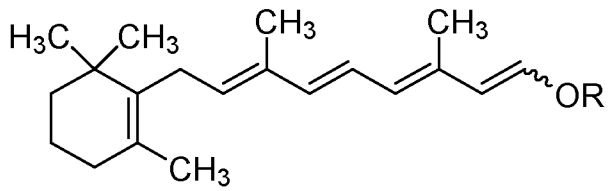
# Novel Enol-Acetates(II)

The present invention relates to new specific enol acetates as well as to their production.

Enol acetates are important intermediates in various organic syntheses.

The new enol acetates we have found are those of formula (I)



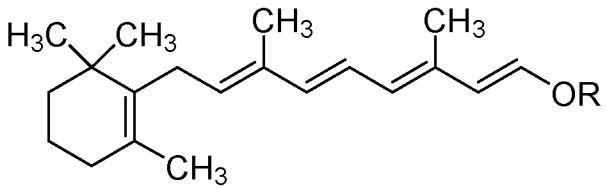

(I)

,

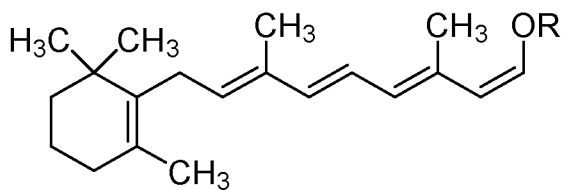
wherein

R is -COR', wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

There are two isomers (compound of formula (Ia) and (Ib))




(Ia)



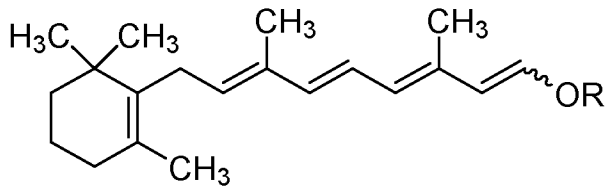

(Ib)

,

wherein

R is -COR', wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

Therefore, the present invention relates to compounds of formula (I)



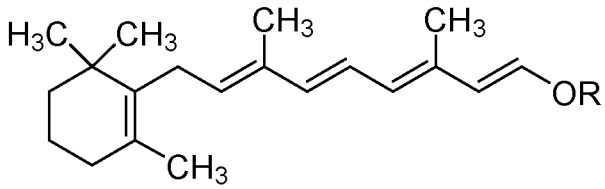

**(I)**

,

wherein

R is -COR', wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

Therefore, the present invention relates to the compounds of formula (Ia)



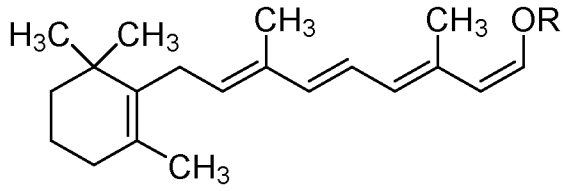

**(Ia)**

,

wherein

R is -COR', wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

Therefore, the present invention related to the compounds of formula (Ib)




**(Ib)**

,

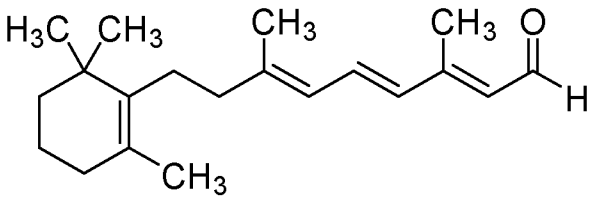
wherein

R is -COR', wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

Due to the C-C-double bonds, there is variety of stereoisomeric forms.

These new enol acetates are important and useful intermediates in organic syntheses (especially in the synthesis of vitamin A and/or its derivatives).

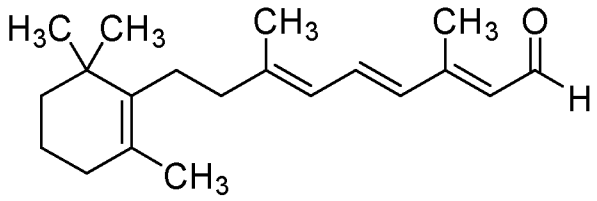
The enol acetate according to the present invention are produced by an enol-acetate formation of the compound of formula (II)



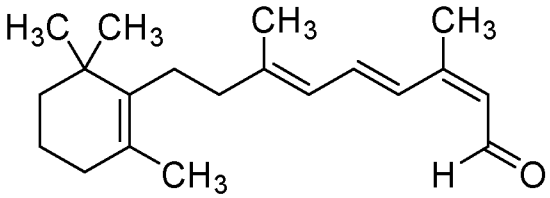

(II)

.

Compound of formula (II) has two isomers (among others) of the following formula (IIa) and (IIb):

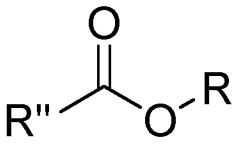



(IIa)




(IIb)

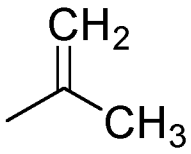
The process is carried out in the presence of at least one acetylating agent, which is a compound of formula (III)




(III)

,

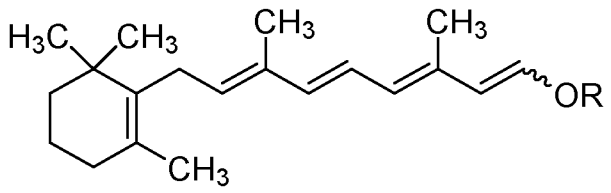
wherein

R is -COR' or  , wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group)

R'' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

Alternatively, the process of the present invention can be carried out in the presence of a transition metal catalyst. Especially in the presence of a Cu catalyst. Especially a Cu(II) catalyst. Very suitable is $Cu(Ac)_2$ as a catalyst.

Therefore, the present invention relates to a process (P) for the production of the compounds of formula (I)

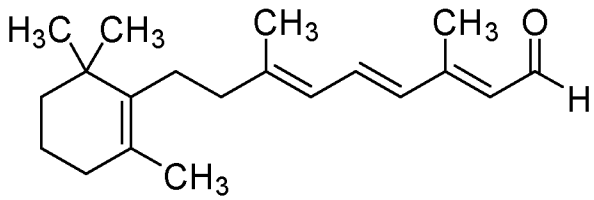
 (I)

,

wherein

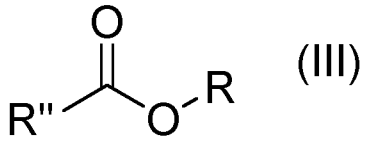
R is -COR', wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group)

by acetylation of a compound of formula (II)

 (II)

,

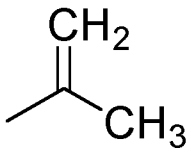
by using at least one acetylating agent of formula (III)



(III)

,

wherein

R is -COR' or  , wherein R' is a $C_1$-$C_{16}$alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group)

R'' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

Alternatively (optionally), the process according to the present invention can be carried out in the presence of at least one transition metal catalyst; especially in the presence of a Cu catalyst. Especially a Cu(II) catalyst. Very suitable is $Cu(Ac)_2$ as a catalyst.

The amount of the catalyst used in the process according to the present invention can vary. The amount of the catalyst usually goes from 0.001 mol-equivalent up to 0.01 mol-equivalent (in relation to compound of formula (II)).

The process according to the present invention is usually carried out in the presence of at least one organic acid or in the presence of a base. Especially in the presence of p-toluenesulfonic acid.

The amount of the acid or of the base can vary. It goes usually from 0.005 mol-equivalent up to 0.1 mol-equivalent (in relation to compound of formula (II)).

The reaction is can be carried out in an inert solvent or the reaction can be carried out without a solvent. Preferably no solvent is used.

The process according to the present is usually carried out at elevated temperatures. Usually the process according to the present invention is carried out at a temperature of from 0°C – 100 °C, preferably from 5°C – 90°C.

As stated above the process according to the present invention is one important step in the synthesis of vitamin A (and/or its derivatives).

The following examples serve to illustrate the invention. The temperature is given in °C and all percentages are related to the weight.

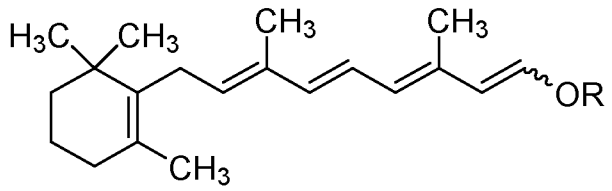
## Examples

Example 1:

A flame-dried 2-necked flask equipped with a reflux condenser was charged with p-toulenesulfonic acid (dry, 0.01 eq), hydroquinone (0.01eq), copper(II)acetate (0.004 eq), isopropenylacetate (2.0 eq) and 3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6-trienal (1.0 eq) in the given order. The reaction mixture was stirred for 3 h at 60 °C, cooled to room temperature and $Et_2O$ (10 mL) was added. The solution was washed with aqueous sat. $NaHCO_3$-solution (5 mL). The aqueous phase was extracted with $Et_2O$ (5 mL) and the combined organic layers were concentrated under reduced pressure (45°C, 2 mbar). The crude material was filtered over silica (first washed with heptane, then with ethylacetate) to afford the product as mixture of isomers.

## Claims

**1.** Compounds of formula (I)




**(I)**

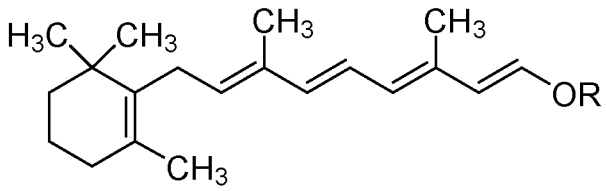
,

wherein

R is -COR',

wherein R' is a $C_1$-$C_{16}$ alkyl group (especially $C_1$, $C_2$ and $C_{15}$).

**2.** Compounds according to claim 1, which has formula (Ia)




**(Ia)**

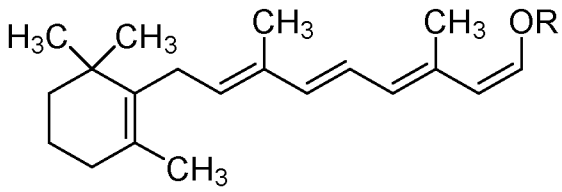
,

wherein

R is -COR',

wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group)

**3.** Compound according to claim 1, which has formula (Ib)




**(Ib)**

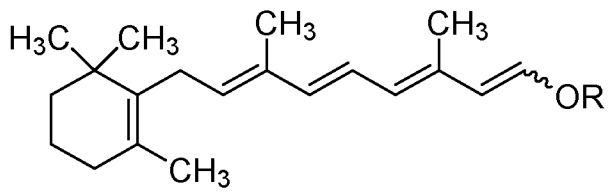
,

wherein

R is -COR',

wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

**4.** Process for the production of the compounds of formula (I) according to claim 1




**(I)**

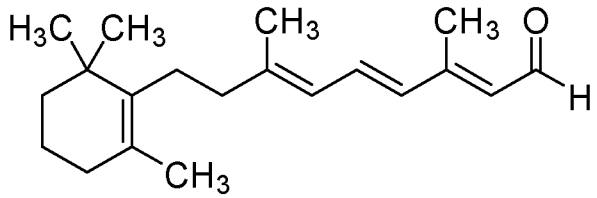
,

wherein

R is -COR',

wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group)

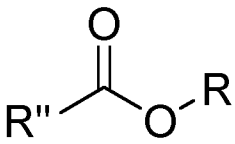
by acetylation of a compound of formula (II)




**(II)**

,

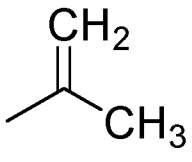
by using at least one acetylating agent of formula (III)




(III)

,

wherein

R is -COR' or 


,

wherein R' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group) and R'' is a $C_1$-$C_{16}$ alkyl group (preferably a $C_1$, $C_2$ or $C_{15}$-alkyl group).

**5.** Process according to claim 4, wherein the process is carried out in the presence of at least one transition metal catalyst.

**6.** Process according to claim 4 or claim 5, wherein the amount of the catalyst is 0.001 mol-equivalent up to 0.01 mol-equivalent (in relation to compound of formula (II)).

**7.** Process according to anyone of the preceding claims 4 - 6, wherein the process is carried out in the presence of at least one organic acid.

**8.** Process according to anyone of the preceding claims 4 - 6, wherein the process is carried out in the presence of at least one base.

**9.** Process according to claim 7 or claim 8, wherein the amount of the acid or base is 0.005 mol-equivalent up to 0.1 mol-equivalent (in relation to compound of formula (II)).

**10.** Process according to anyone of the preceding claims 4 - 9, wherein the process is carried out in an inert solvent.

**11.** Process according to anyone of the preceding claims 4 - 9, wherein the process is carried out without any solvent.

**12.** Process according to anyone of the preceding claims 4 - 11, wherein the process is carried out at a temperature of from 0°C – 100°C (preferably from 5°C – 90°C).

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/059482

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C403/12
ADD.

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)
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 practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | EP 1 031 561 A1 (HOFFMANN-LA ROCHE)<br>30 August 2000 (2000-08-30)<br>claim 1<br>----- | 1-3<br>4-12 |
| Y | D. FAVARA, ET AL.: "A facile synthesis of trans<br>(+)-4-carboxymethyl-3-ethylazetidin-2-one and its conversion into natural PS-5",<br>TETRAHEDRON LETTERS,<br>vol. 23, no. 30, July 1982 (1982-07),<br>pages 3105-3108, XP055393165,<br>Elsevier Science Publishers, Oxford, GB<br>ISSN: 0040-4039, DOI:<br>10.1016/S0040-4039(00)87545-0<br>page 3105, last paragraph - page 3106,<br>paragraph 1; compounds 3, 4<br>-----<br>-/-- | 4-12 |

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

[X] See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 8 June 2020 | 23/06/2020 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | English, Russell |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | C. FEHR, ET AL.: "The synthesis of (Z)-trisubstituted allylic alcohols by the selective 1,4-hydrogenation of dienol esters: improved synthesis of (-)-beta-santalol", CHEMISTRY - A EUROPEAN JOURNAL, vol. 17, no. 4, 7 December 2010 (2010-12-07), pages 1257-1260, XP055007610, Wiley-VCH Verlag, Weinhem, DE ISSN: 0947-6539, DOI: 10.1002/chem.201002729 compounds 11, 13, 18, 19, 22, 23, 25, 26, 28, 29, 31, 32 ----- | 4-12 |
| Y | W.J. BAILEY, ET AL.: "Pyrolysis of esters. V. Mechanism of 1,4-elimination", JOURNAL OF ORGANIC CHEMISTRY, vol. 21, no. 3, 1 March 1956 (1956-03-01), pages 328-331, XP055701508, American Chemical Society, Washington, DC, US ISSN: 0022-3263, DOI: 10.1021/jo01109a017 page 330, lines 23-49; compound X ----- | 4-12 |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/059482

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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