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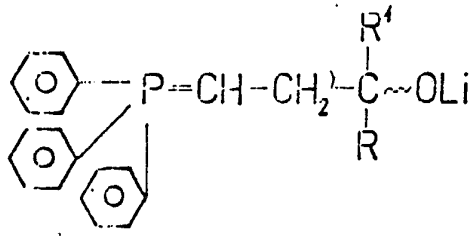
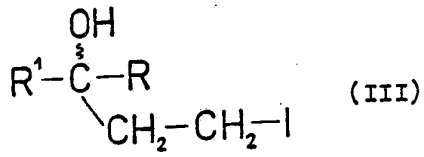
(54) Title: NOVEL PROSTAGLANDIN INTERMEDIATES MODIFIED IN THE ω-CHAIN AND PROCESS FOR PREPARING SAME



(I)



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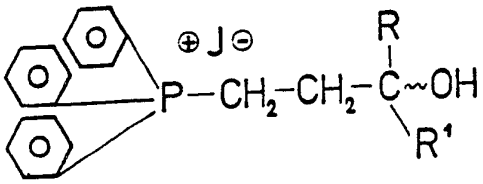

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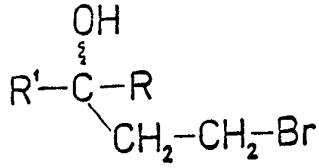

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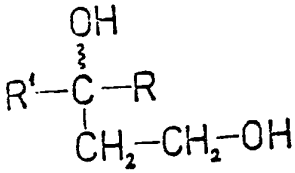

(V)

(57) Abstract

The invention relates to the preparation of compounds of formula (I), wherein R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or cyclohexyl group; and R^1 stands for a C_{1-4} alkyl group. The invention relates also to the new intermediates of formula (II), formula (III), formula (IV) and formula (V).

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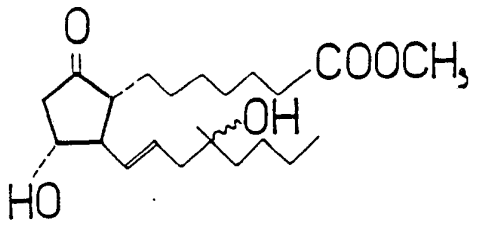
NOVEL PROSTAGLANDIN INTERMEDIATES MODIFIED IN THE ω-CHAIN AND PROCESS FOR PREPARING SAME

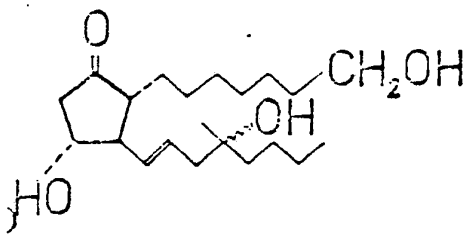
This invention relates to novel prostaglandin intermediates. According to an other aspect of the invention, there is provided a process for the preparation of these compounds.

It is known that several prostaglandin-E (PGE) derivatives exert a remarkable gastric secretion-inhibiting and cytoprotective effect. Such compounds are e.g. misoprostol of the formula (VIII)



(VIII)

and rioprostil of the formula (IX)

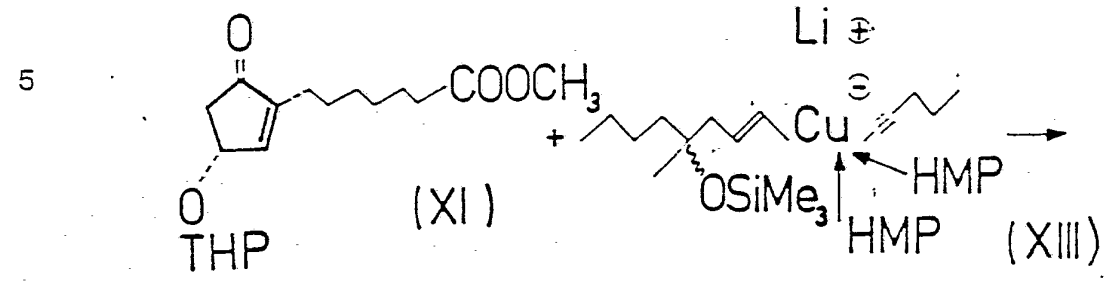


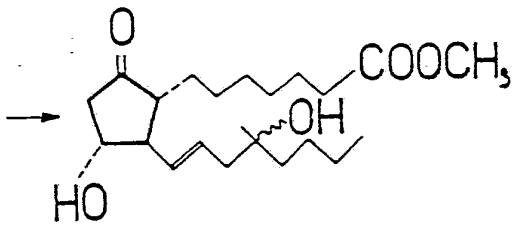
(IX)

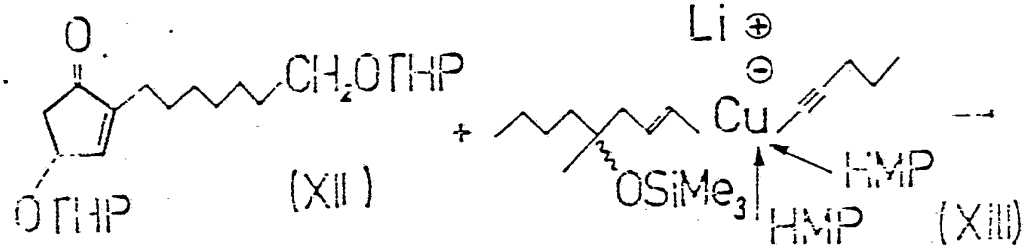
[Drugs of the Future 2, 817 (1977); ibid. 10, 207 (1985)].

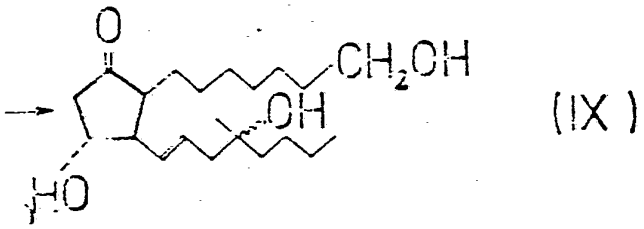
The above compounds are prepared in a way known from the literature [Tetrahedron Lett. 48, 4217 (1975); as well as US-PS No. 4,132,738] according to the Scheme A)

Scheme A)

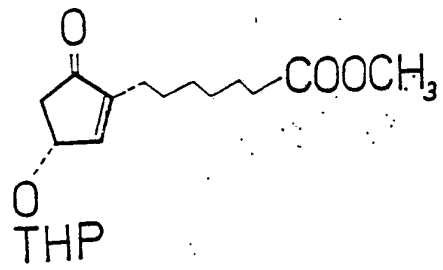

O
COOCH3
O
THP
(XI)
Li ⊕
⊖
Cu
OSiMe3
HMP
HMP
(XIII)


O
COOCH3
OH
HO
(VIII)


O
CH2OTHP
OTHP
(XII)
Li ⊕
⊖
Cu
OSiMe3
HMP
HMP
(XIII)

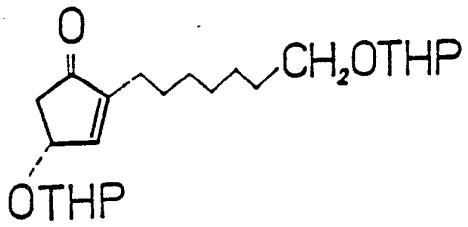

O
CH2OH
OH
HO
(IX)

via a conjugate addition of a cyclopent-1-enealkane-carboxylic acid ester of the formula (XI)



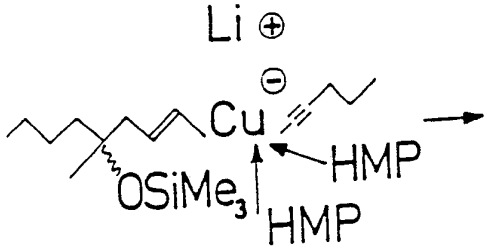
(XI)

or cyclopent-1-enealcohol of the formula (XII)



(XII)

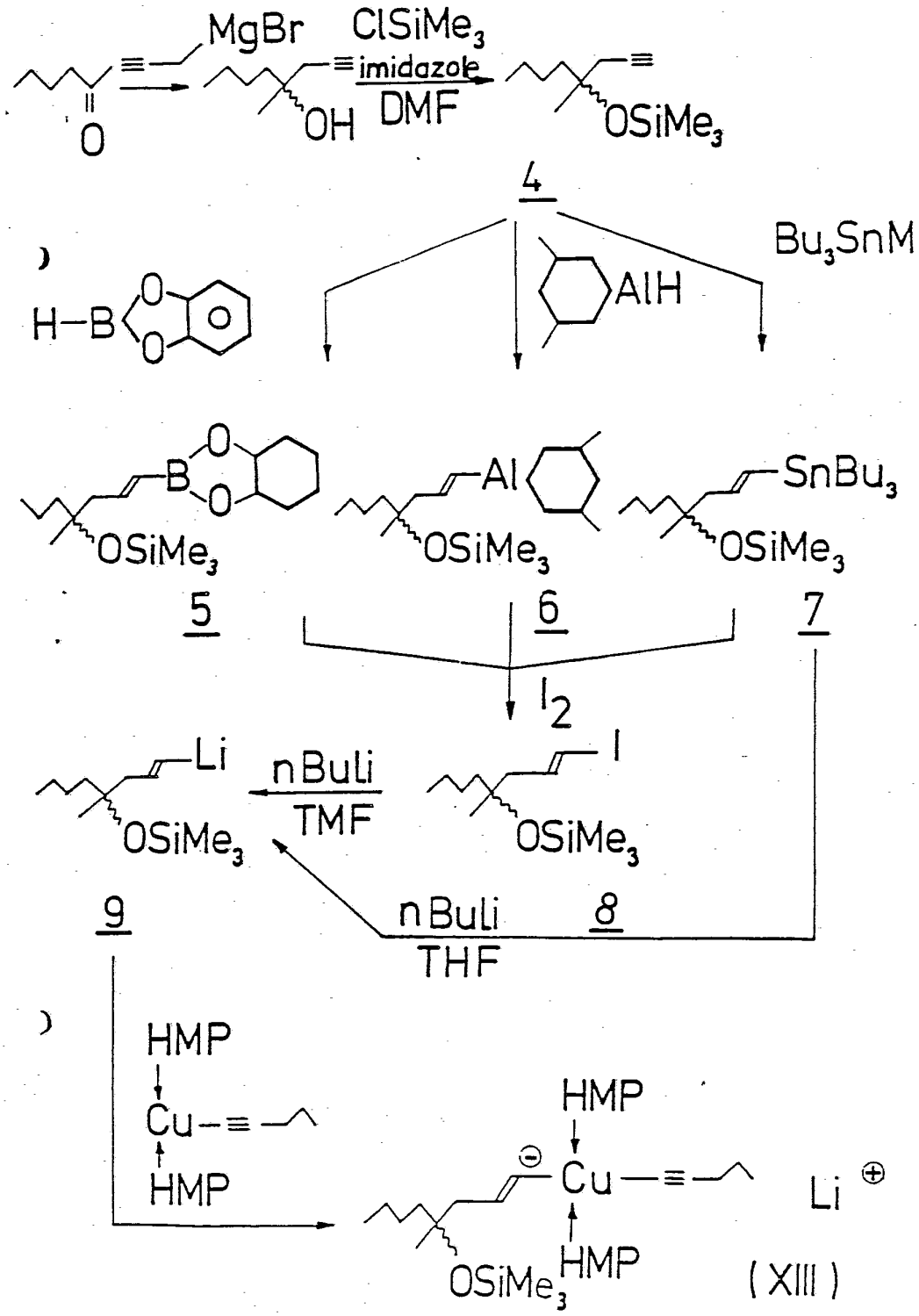
protected by tetrahydropyranyl (THP) group, with the vinyl cuprate reagent of the formula (XIII)



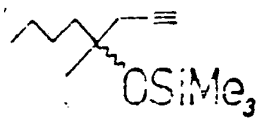
(XIII)

The preparation of the vinyl cuprate of the formula (XIII) is known from the literature [J. Med. Chem. 20, 1152 (1977); as well as BE-PS No. 827,127 and US-PS No. 4,087,447] as shown in Scheme B).

Scheme B

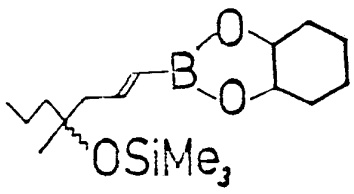


According to Scheme B) the trimethylsilyl--protected 4-methyl-1-octine-4(RS)-ol of the formula (4)

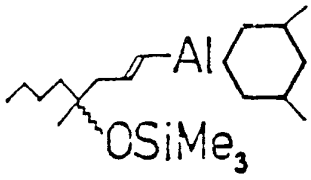


(4)

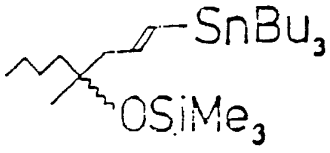
which can be obtained by reacting 2-hexanone with propargylmagnesium bromide in a Grignard reaction followed by trimethylsilylation, is transformed through stereoselective hydroboration, hydroalumination or hydrostannation to the corresponding trans-vinylborane, -alane or -stannane compounds of the formula (5), (6) or (7), respectively



(5)



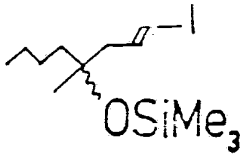
(6)



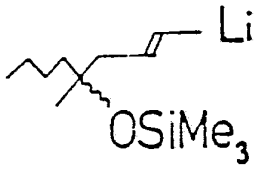
(7)

from which the corresponding trans-iodoalkene of the formula (8)

(8)

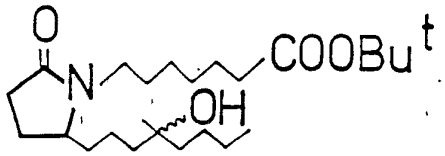


is obtained with elementary iodine. From the thus obtained iodoalkene of the formula (8) or vinylstannane of the formula (7), the appropriate trans-vinyllithium compound of the formula (9)



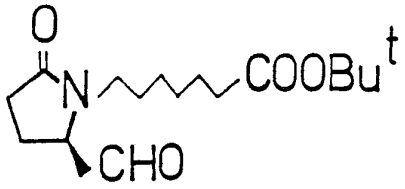
(9)

is prepared by transmetalation carried out with n-butyllithium. The vinyl cuprate reagent of the formula (XIII) is obtained by reacting a tetrahydrofuran solution of the vinyllithium compound of the formula (9) with an ethereal solution of copper(I)pentyne solvated with hexamethylphosphoric acid triamide (HMP). In addition to the complicateness, the carrying out of these reactions requires very high accuracy, particular conditions, extreme purity and anhydrousness of the reagents and solvents. A more recent synthesis of the compounds of formulae (VIII), (IX) and (XIV)



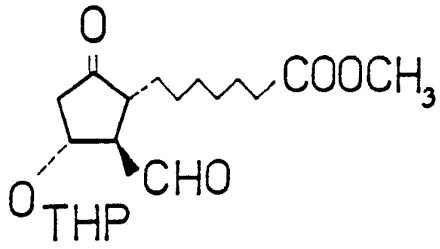
(XIV)

may be achieved in such a way that the ω-chain is built up by reacting the compound of the formula (XV)



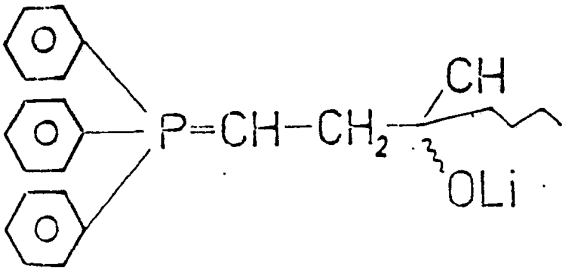
(XV)

or formula (XVI)



(XVI)

with the phosphorane of the formula (Ia)

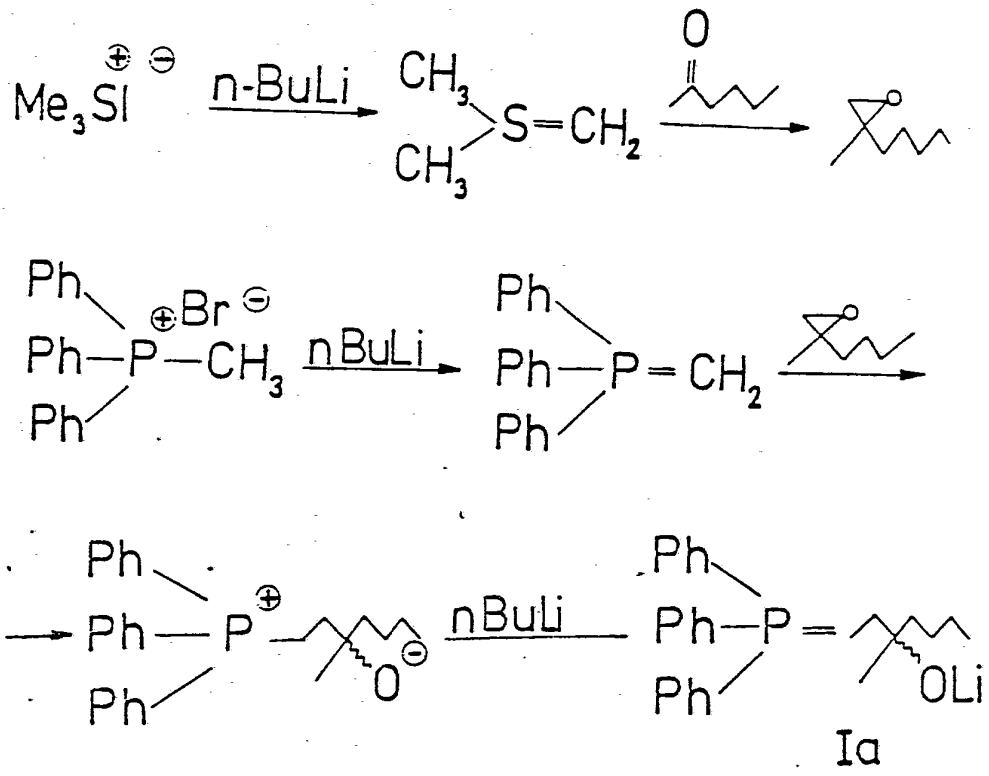


(Ia)

in a trans-selective Witting reaction [Tetrahedron Lett. 23, (10) 1067 (1982)].

The phosphorane of the formula (Ia) may be prepared according to Scheme C)

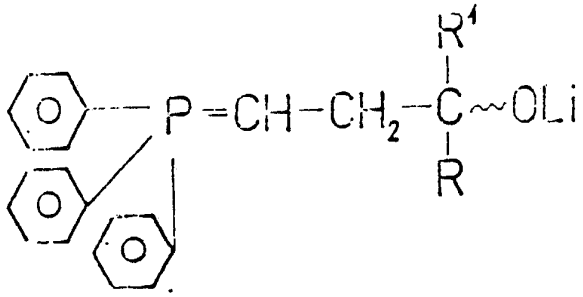
Scheme C)



wherein all the intermediates of the reaction series are unisolable reactive substances whereby any way of purification is excluded.

It is obvious that the known solutions involve important drawbacks from the viewpoint of an industrial realization.

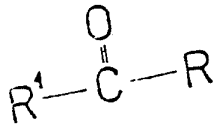
In order to eliminate these disadvantages, a novel method has been sought for preparing the intermediates of the formula (I)



(I)

and (Ia).

Surprisingly, it has been found that the intermediates of the formula (I) can be obtained by reacting an oxo compound of the formula (VII),



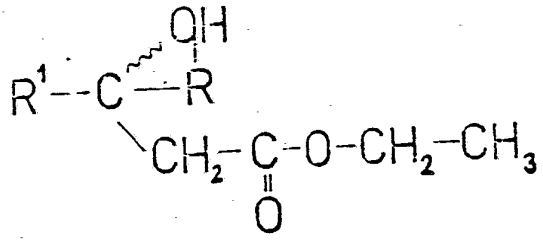
(VII)

wherein

R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or cyclohexyl group; and

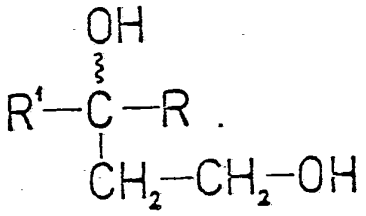
R^1 means a C_{1-4} alkyl group,

with a C_{1-6} alkyl bromoacetate and zinc powder (Reformatskii synthesis); then reacting the thus obtained compound of the formula (VI),



(VI)

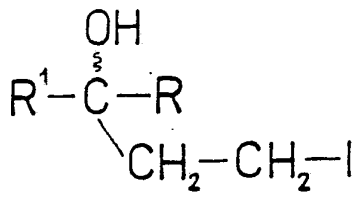
wherein R and R^1 are the same as defined above, with a metal hydride; reacting the thus prepared compound of the formula (V),



(V)

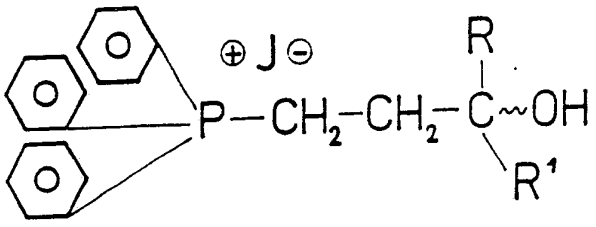
wherein R and R^1 are the same as defined above, with triphenylphosphine and carbon tetrabromide; then transforming the obtained compound of the formula (IV),

wherein R and R^1 are the same as defined above, with an inorganic iodine compound; reacting the thus obtained compound of the formula (III),



(III)

wherein R and R^1 are the same as defined above, with triphenylphosphine; and transforming the thus prepared novel phosphonium salt of the formula (II)



(II)

with 2 molar equivalents of an alkyllithium or lithium alkylamide type compound in one step to give the intermediate of the formula (I).

A preferred embodiment of the process of the invention is as follows.

A compound of the formula (VII) is reacted with zinc metal and ethyl bromoacetate or an other C_{1-6} alkyl bromoacetate in tetrahydrofuran or in an other solvent commonly used in the Reformatskii synthesis. The resulting compound of the formula (VI) is reduced by a complex metal hydride, preferably by

lithium aluminium hydride (LAH) in tetrahydrofuran or in an other solvent, commonly used in the metal hydride reductions. Thereafter, the primary hydroxyl group of the resulting compound of formula (V) is replaced by bromine by using a system consisting of carbon tetrabromide and triphenylphosphine in acetonitrile solvent, whereafter bromine in the thus prepared compound of the formula (IV) is replaced by iodine by using an alkaline metal iodide, preferably sodium iodide in acetone medium to give a compound of the formula (III) which in turn is refluxed with 10 to 15 molar equivalents of triphenylphosphine in acetonitrile to give a phosphonium salt of the formula (II).

The compounds of the formulae (VI), (V) (IV), (III) and (II) prepared according to our invention are stable and can be isolated thus, their purification can advantageously be achieved. The compounds of the formulae (III) to (VI) may be purified by distillation or chromatography whereas the salt-like compounds of the formula (II) are purified by chromatography or recrystallization.

The compounds of the formulae (II) to (V) prepared according to our invention are novel.

An additional and unexpected advantage of the reaction route of the invention consists in that the compounds of the formula (V) are most easy to selectively brominate in a nearly quantitative yield while the tertiary hydroxyl group remains unchanged.

As mentioned hereinbefore, the compounds of the formula (II) can be transformed to compounds of the formula (I) by using 2 molar equivalents of an alkyllithium or lithium alkylamide type compound . Lithium iodide arising as a side product in this reaction increases the trans-selectivity of the Wittig reaction of the compounds of formulae (XV), (XVI) or (XVII) with

the compound of the formula (I) [Tetrahedron Lett. 26, (3) 311 (1985); J. Am. Chem. Soc. 103, 2823 (1981); as well as Liebigs Ann. Chem. 708, 1 (1967)].

The process of the invention is illustrated in detail by the following non-limiting Examples.

Example 1

Ethyl 3(R,S)-hydroxy-3-methylheptanoate

27.5 ml of ethyl bromoacetate and 35 ml of 2-hexanone are simultaneously portionwise added to a suspension of 17.5 g of dry zinc powder in 150 ml of abs. tetrahydrofuran at the boiling temperature within 30 minutes (the reaction is exothermic). After the addition, the reaction mixture is refluxed for additional 90 minutes, then cooled to room temperature and decomposed by adding a mixture of 100 ml of water and 20 ml of acetic acid at such a rate that the temperature does not exceed 30 °C. After the decomposition, the phases are separated and the aqueous phase is extracted 3 times with 80 ml of ethyl acetate each. After that the solvent is removed from the combined organic phases, which are then subjected to fractional distillation to give 35.3 g (76%) of the title compound, b.p. 68-70 °C at 2 Hgmm.

^{1}H-NMR ($CDCl_3$, with TMS as internal standard, δ ppm):

0.9 t (3H); 1-1.5 m (11H); 2.5 s (3H); 3.5 s (1H); 4.2 q (2H).

Example 2

2(R,S)-Hydroxy-2-(2-hydroxyethyl)hexane

2 g of lithium aluminium hydride are carefully added in little portions to a solution of 9 g of ethyl 3(R,S)-hydroxy-3-methylheptanoate in 50 ml of abs. tetrahydrofuran at room temperature, then the temperature is increased to 40 °C and the reaction is followed by chromatography [with a developing system of a 4:1 vol./vol. mixture of hexane and ethyl acetate on a Kieselgel

60 F_{254} (Merck) sheet, by detecting with an 5% ethanolic phosphomolybdenic acid solution with heating to 150 °C; the R_f value of the starting material is 0.4, that of the title product is 0.1]. When no starting material may be observed in the reaction mixture, the reaction mixture, the excess lithium aluminium hydride is decomposed by adding 10 ml of ethyl acetate and then diluted (carefully) with 50 ml of water. The precipitated lithium and aluminium salts are filtered off and the phases of the mother liquor are separated. The aqueous phase is extracted 3 times with 20 ml of ethyl acetate each, the organic phases are combined and the solvent is removed. The residue is purified by column chromatography to give 5.7 g (82%) of the title compound.

^1H-uncoupled ^{13}C-NMR ($CDCl_3$ with TMS as internal standard, δ ppm): 14.1; 23.3; 26.3; 26.5; 41.4; 42.3; 59.4; 73.4; 73.8.

Example 3

2-(2-Bromoethyl)-2(R,S)-hydroxyhexane

4.7 g of triphenylphosphine are added to a solution of 2.4 g of 2(R,S)-hydroxy-(2-hydroxyethyl)-hexane in 10 ml of acetonitrile. Then, 5.1 g of carbon tetrabromide are portionwise added to the suspension obtained at room temperature, the reaction solution is stirred for 3 hours. The reaction is followed by chromatography (under the same conditions as described in Example 2, the R_f value of the title compound is 0.5). At the end of the reaction, the solvent is removed and the residue is purified by column chromatography with a column of 2 cm in diameter, with a charge height of 20 cm of Kieselgel 60 F_{254} (Merck); a 4:1 vol./vol. mixture of hexane and ethyl acetate is used as eluent under a pressure of 2 bar. Thus 3.3 g (97%) of the title compound are obtained.

^{1}H-NMR ($CDCl_3$ with TMS as internal standard, δ ppm):
0.9 t (3H); 1.2 s (3H); 1.2-1.5 m (7H);
1.95-2.2 m (2H); 3.4-3.6 m (2H).

Example 4

2(R,S)-Hydroxy-2-(2-iodoethyl)hexane

A solution containing 2.1 g of 2-(2-bromoethyl--2(R,S)-hydroxy-hexane in 10 ml of acetone saturated with sodium iodide is refluxed for 30 minutes, then the acetone is distilled off. The residue is taken up in 15 ml of n-hexane, filtered and the salts filtered out are washed 3 times with 10 ml of n-hexane each. The combined n-hexane phases are evaporated to give 2.3 g (90 %) of the title compound.

^{1}H-NMR ($CDCl_3$ with TMS as internal standard, δ ppm):
0.92 t (3H); 1.17 s (3H); 1.2-1.6 m (7H);
2.03-2.22 m (2H); 3.15-3.35 m (2H)

^{1}H-uncoupled ^{13}C-NMR ($CDCl_3$ with TMS as internal standard, δ ppm): -0.55; 14.0; 23.1; 25.0; 25.3; 41.6; 46.8; 74.0.

Example 5

3(R,S)-Hydroxy-3-methyl-1-heptyl-triphenylphosphonium iodide

A mixture containing 2 g of 2(R,S)-hydroxy--2-(2-iodoethyl)hexane, 20 g of triphenylphosphine and 20 ml of acetonitrile is refluxed for 8 hours, then the disappearance of the starting material is observed by chromatography (under the same conditions as described in Example 2, the R_f value of the starting iodine compound is 0.5). At the end of the reaction, the mixture is cooled to room temperature, triphenylphosphine is filtered off and washed twice with 20 ml of acetonitrile each. The acetonitrile washings and the mother liquor are combined and the solvent is removed. The residue is purified by removing the excess triphenylphosphine with chromatography on the column

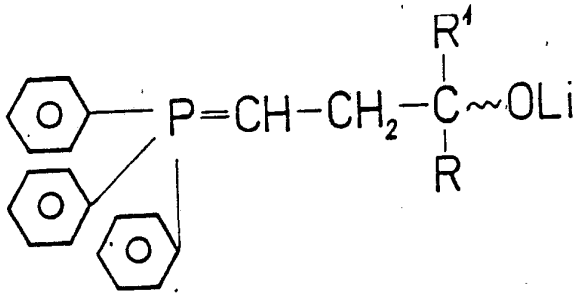
ard under conditions described in Example 3. Triphenylphosphine is eluted by ethyl acetate then, the title product is eluted by a 2:1 vol./vol. mixture of acetone and ethyl acetate. Thereafter, the solvent is carefully evaporated from the product under reduced pressure which is then crystallized while stirring with hexane at room temperature. Thus 3.4 g (84%) of the title compound are obtained, m.p.; 128-130 °C.

^{1}H-NMR ($CDCl_3$ with TMS as internal standard, δ ppm):
0.85 t (3H); 1.3 s (3H); 1.4-1.9 m (8H);
3.4-3.85 m (3H); 7.7-8 m (15 H)

^{1}H-uncoupled ^{13}C-NMR ($CDCl_3$ with TMS as internal standard, δ ppm): 14.1 (C_7); 17.5; 19.6 (C_2);
23.0 (C_6); 26.1; 25.2 (C methyl); 33.9;
34.0 (C_4); 41.5 (C_5); 71.8; 72.3 (C_3);
116.4; 119.8 (C_1); 130.4; 130.8; 133.3; 133.7;
135.2 ($C_{aromatic}$).

Claims

1. A process for the preparation of compounds of the formula (I),



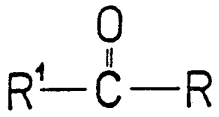
(I)

wherein

R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or cyclohexyl group; and

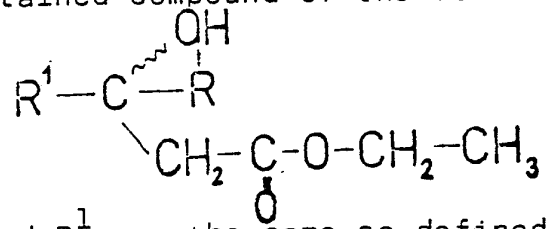
R^1 stands for a C_{1-4} alkyl group,

which comprises reacting a compound of the formula (VII),



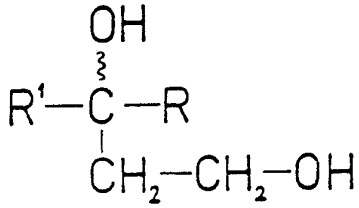
(VII)

wherein R and R^1 are the same as defined above, with zinc metal and a C_{1-6} alkyl bromoacetate; then reacting the thus obtained compound of the formula (VI)



(VI)

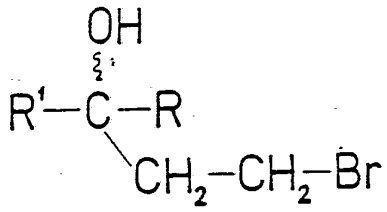
wherein R and R^1 are the same as defined above, by a metal hydride; reacting the thus prepared compounds of the formula (V),



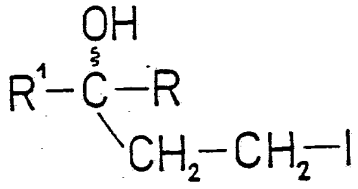
(V)

wherein R and R^1 are the same as defined above, with triphenylphosphine and carbon tetrabromide; transforming the obtained compound of the formula (IV),

(IV)

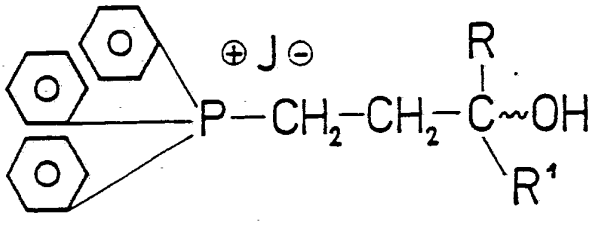


wherein R and R^1 are the same as defined above, with an inorganic iodine compound; bringing into reaction the thus obtained iodine compound of the formula (III),



(III)

wherein R and R^1 are the same as defined above, with triphenylphosphine; and reacting the thus prepared phosphonium salt of the formula (II),



(II)

wherein R and R^1 are the same as defined above, with an alkyllithium or a lithium alkylamide type compound to give the compound of the formula (I),

2. A process as claimed in claim 1, which

comprises reacting a compound of the formula (VII) with ethyl bromcacetate and zinc metal in an anhydrous organic solvent.

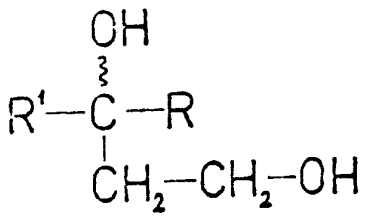
3. A process as claimed in claim 1, which comprises using lithium aluminium hydride as a metal hydride.

4. A process as claimed in claim 1, which comprises reacting a compound of the formula (V) with triphenylphosphine and carbon tetrabromide in an organic solvent, preferably in acetonitrile.

5. A process as claimed in claim 1, which comprises using an alkaline metal iodide, preferably sodium iodide as an iorganic iodine compound.

6. A process as claimed in claim 1, which comprises transforming a compound of the formula (II) to a compound of the formula (I) by using an alkyllithium compound containing a C_{1-6} alkyl group or a C_{1-10} lithium dialkylamide or cycloalkylalkylamide compound.

7. Compounds of the formula (V),



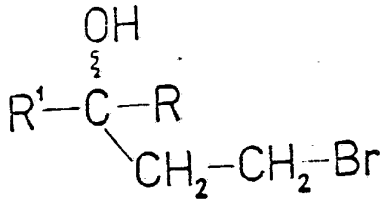
(V)

wherein

R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or cyclohexyl group; and

R^1 stands for a C_{1-4} alkyl group.

8. Compounds of the formula (IV),



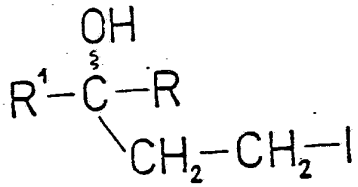
(IV)

wherein

R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or cyclohexyl group; and

R^1 stands for a C_{1-4} alkyl group.

9. Compounds of the formula (III),



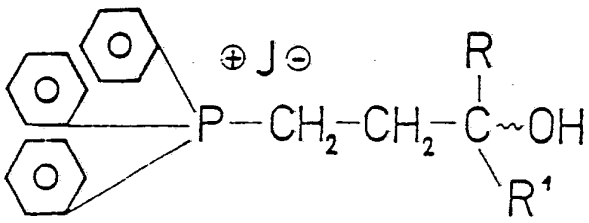
(III)

wherein

R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or cyclohexyl group; and

R^1 stands for a C_{1-4} alkyl group.

10. Compounds of the formula (II),



(II)

wherein

R means a straight or branched chain C_{1-6} alkyl group optionally substituted by a cyclopentyl or cyclohexyl group; or a cyclopentyl or a cyclohexyl group; and

R^1 stands for a C_{1-4} alkyl group.

11. 2(R,S)-Hydroxy-2-(2-hydroxyethyl)hexane.

12. 2-(2-Bromoethyl)-2(R,S)-hydroxyhexane.

13. 2(R,S)-Hydroxy-2-(2-iodoethyl)hexane.

14. 3(R,S)-Hydroxy-3-methyl-1-heptyl-triphenyl-phosphonium iodide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 88/00016

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 F 9/535; C 07 C 31/20,31/36

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
Int.Cl.[4]	C 07 F 9/535; C 07 C 31/00,31/18,31/20,31/34,31/36

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

CAS online

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Tetrahedron Letters, vol. 23, no. 10, issued 1982, Chia-Lin J. Wang "Azaprostanoids I. Synthesis of (rac)-8-aza-11-deoxy-15-deoxy-16 hydroxy-16-methylprostagandins" 1067-1070, see pages 1068,1069.	(1)
A	Journal of Organic Chemistry, vol. 43, no. 4, issued 1978, W.G.Salmond et al. "A stereo-selective Wittig reagent and its application to the synthesis of 25-hydroxylated vitamin D metabolites", 790-792, see page 790.	(1)
X A	Soviet Inventions Illustrated, section Ch, week C44, 720,773-724,077, issued 1980, December 10, Derwent Publications Ltd. London 1980, Pharmaceuticals p.2, see abstract-no. 78 517 C/44, SU-722 893 (UFA PETROLEUM INST).	(7) (11)
X A	Patent Abstracts of Japan, unexamined applications, C field, vol. 8, no. 130 (C229) [1567] issued 1984, June 16, The Patent Office Japanese Government, see page 107 C 229, JP-A-59-042 330, 8.3.1984 (SUNTORY K.K.).	(7) (11)

* Special categories of cited documents: [10]

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

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

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

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

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

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

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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 May 1988 (10.05.88)	27 May 1988 (27.05.88)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X A	Soviet Inventions Illustrated, section Ch: Chemical, week 8416, 784 502-1 030 028, issued 1984, May 30, Derwent Publications Ltd., London 1984, see abstract-no. 84-099 870/16, E16, SU-1 028 657 A (AS UKR PHYS CHEM IN).	(8) (12)
X,P A	Soviet Inventions Illustrated, section Ch: Chemical, week 8737, 421 304-1 288 505, issued 1987, October 28, Derwent Publications Ltd., London 1987, see abstract-no. 87 262 303/37, SU 1 286-588 A (UFA PETROLEUM INST).	(9) (13)

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No.PCT/HU 88/00016

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
SU-A - 722 893	25/03/1980	None	
JP-A2-59-042 330	08/03/1984	None	
SU-A - 1 028 657	15/07/1983	None	
SU-A - 1 286 588	07/02/1987	None	