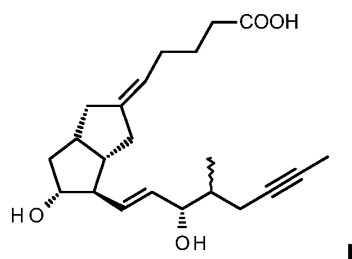


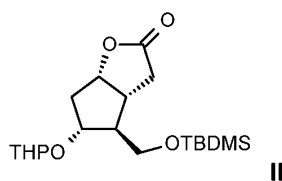
Claims

1. Process for the preparation of iloprost of formula I



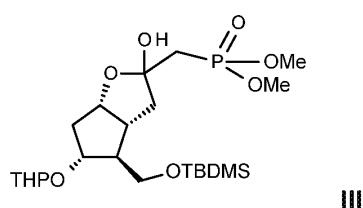
comprising that

- a.) the Corey lactone of formula II



is selectively alkylated with dimethyl methylphosphonate in the presence of lithium dialkylamide,

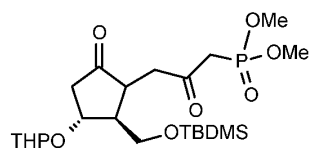
- b.) the ring of the resulting lactol of formula III



is opened with pyridinium acetate in weak acidic medium, then the obtained secondary hydroxyl group is oxidized with pyridinium dichromate,

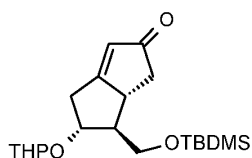
- c.) the resulting compound of formula IV

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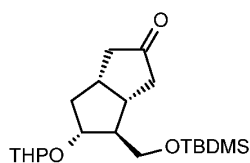
IV

is reacted with potassium carbonate in the presence of 18-crown-6 reagent,
d.) the thus obtained compound of formula V



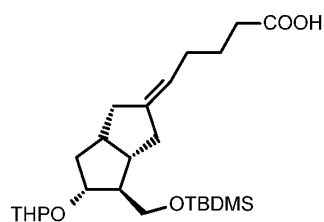
V

is reduced,
e.) the resulting compound of formula VI



VI

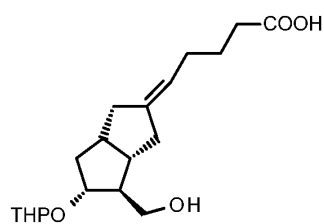
is reacted with carboxybutyltriphenylphosphonium bromide in the presence of potassium
tertiary-butyrate,
f.) the TBDMS protecting group of the resulting E- and Z- isomers of formula VII



VII

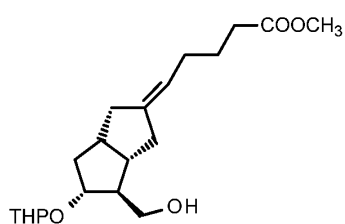
is removed, the isomers are separated by gravitational chromatography, if desired the Z-
isomer (VII_{lz}) is isomerized into the E-isomer,
g.) the resulting compound of formula VIII

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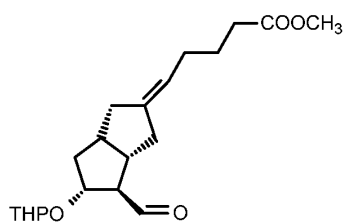
VIII

is esterified,
h.) the resulting compound of formula IX



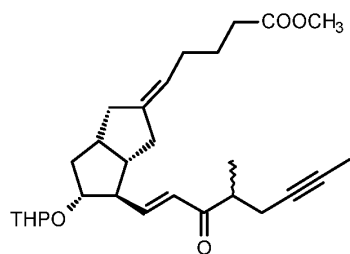
IX

is oxidized,
i.) the resulting compound of formula X



X

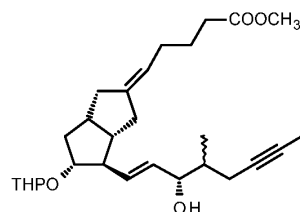
is transformed in HWE reaction in the presence of solid potassium hydroxide into the compound of formula XI,
j.) the oxo group of the resulting compound of formula XI



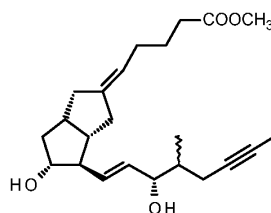
XI

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is reduced with DIBAL-F,
k.) the tetrahydropyranyl protecting group of the thus obtained compound of formula **XII**

**XII**

is removed and the compound is purified by gravitational column chromatography, if
desired further purified by preparative HPLC,
l.) the ester group of the resulting compound of formula **XIII**

**XIII**

is removed and the obtained compound of formula **I** is purified.

2. Process according to claim 1 wherein the lithium dialkylamide is lithium diisopropylamide or lithium dicyclohexylamide in step a).
3. Process according to claim 1 or 2 wherein the reaction in step c) is carried out in high dilution, preferably in 30-45-fold dilution, at high temperature, preferably at 90-110°C.
4. Process according to any of claims 1 to 3 wherein the reaction in step c) is carried out in a way that the solution of the compound of formula **IV** is added dropwise into the refluxing solution of the reagents.
5. Process according to any of claims 1 to 4 wherein the removal of the silyl protecting group in step f) is effected with tetrabutylammonium fluoride trihydrate.
6. Process according to any of claims 1 to 5 wherein the separation of the E- and Z- isomers in step f) is carried out applying step-gradient eluent mixtures, using toluene: methyl tertiary-butyl ether mixture as eluent.
7. Process according to any of claims 1 to 6 wherein the isomerisation of the Z- isomer in step f) is carried out by irradiation in the presence of dimethyl disulfide sensibiliser.
8. Process according to any of claims 1 to 7 wherein the oxidation in step h) is carried out by Pfitzner-Moffatt oxidation with phosphoric acid-DMSO mixture containing DCC or DIC, or by Anelli oxidation (sodium hypochlorite, TEMPO catalyst).
9. Process according to any of claims 1 to 8 wherein the compound of formula **X** is transformed in step i) into compound of formula **XI** without isolation.

10. Process according to any of claims 1 to 9 wherein in step i) the 15R isomer of formula **XIIb**, separated by chromatography, after oxidation and THP-protection of the 11-OH group is recycled into the synthesis.
11. Process according to any of claims 1 to 10 wherein the compound of formula **XII** is not isolated in step k).
12. Process according to any of claims 1 to 11 wherein the crude final product of formula **I** is purified by gravitational chromatography and/or preparative HPLC.
13. Process for the preparation of the solid form of the compound of formula **I** comprising that the purified oily compound of formula **I** is dissolved in the same amount of polar solvent as the mass of the oily product, and such an amount of alkane is added to it that the solution turns opalescent, the solution is then solidified glassy at a temperature from (-)60°C to (-)20°C and the solvent is removed in high vacuum.
14. Process according to claim 13 wherein the polar solvent is acetone, ethyl acetate, methyl ethyl ketone or isopropanol.
15. Process according to claim 13 or 14 wherein the alkane is pentane, n-hexane, cyclohexane or heptane.
16. The compound of formula **X**.
17. The compound of formula **XI**.
18. The compound of formula **XII**.
19. Solid phase iloprost.
20. Solid phase iloprost in the form of amorphous powder.
21. Iloprost having a purity of at least 93 mass%.
22. Iloprost having a purity of at least 95.0 mass%.
23. Iloprost having a purity of at least 98.0 mass%.
24. Iloprost having a purity of at least 98.5 mass%.
25. Iloprost having a purity of at least 95.0 mass%, wherein the total amount of the impurities related to iloprost is not more than 3.5 mass% and the total amount of non-identified impurities is not more than 2.5 mass%.
26. Iloprost having a purity of at least 98.0 mass%, wherein the total amount of the impurities related to iloprost is not more than 1.6 mass%, the total amount of non-identified impurities is not more than 1.0 mass% and the amount of non-identified impurities, each is not more than 0.1 mass%.
27. Iloprost having a purity of at least 98.5 mass%, wherein the total amount of the impurities related to iloprost is not more than 1.6 mass%, the total amount of non-identified impurities is not more than 0.5 mass% and the amount of non-identified impurities each, is not more than 0.1 mass%.
28. Crystalline 16(S)-iloprost.
29. Compound of formula (S)-**XII**.
30. Compound of formula (R)-**XII**.
31. Process according to claim 1 for the preparation of 16(S)-iloprost comprising that the compound of formula **X** is reacted with (S)-ILO-phosphonate.
32. Process according to claim 1 for the preparation of 16(R)-iloprost comprising that the compound of formula **X** is reacted with (R)-ILO-phosphonate.
33. Iloprost having a purity of at least 98.5 mass% in the form of crystal.