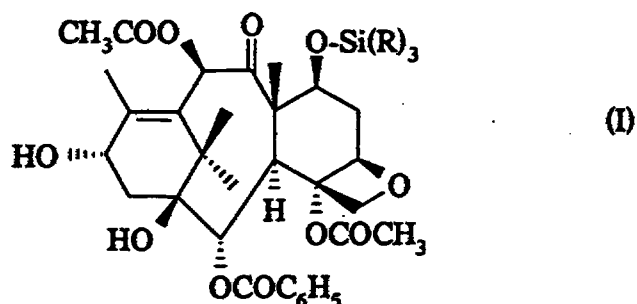


PROCESS FOR THE PREPARATION OF 7-TRIALKYLSILYLBACCATINIII

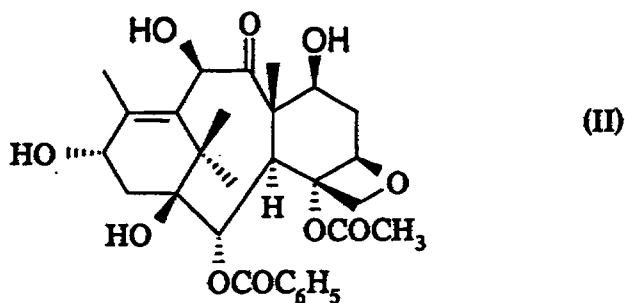
The present invention relates to a novel process for the preparation of 7-trialkylsilylbaccatin

5 III of general formula:



in which the symbols R, which may be identical or different, represent alkyl radicals containing 1 to 4 carbon atoms which are optionally substituted with a phenyl radical, starting with 10-deacetylbaccatin III

10 of formula:



In the general formula (I), each of the symbols R preferably represents a straight or branched alkyl radical containing 1 to 4 carbon atoms. Even more particularly, each of the symbols R represents an ethyl radical.

15 radical.

It is known, in particular according to J-N. Denis and A. E. Greene, J. Amer. Chem. Soc., 110, 5917-5919 (1998), to prepare a product of general formula (I) from 10-deacetylbaecatin III of formula (II) by first carrying out the selective silylation at position -7 of the taxane ring system in order to obtain 7-trialkylsilyl-10-deacetylbaecatin III, and then by selectively acetylating at position -10 the 7-trialkylsilyl-10-deacetylbaecatin III thus obtained.

According to the known process, the silylation reaction is carried out by treating 10-deacetylbaecatin III with excess trialkylsilyl halide of general formula:



in which Hal represents a halogen atom and R is defined as above, working in a basic organic solvent such as pyridine, at a temperature in the region of 20°C. Generally, 7-trialkylsilyl-10-deacetylbaecatin III is obtained with a yield in the region of 85%.

According to the known process, the acetylation is carried out by treating 7-triethylsilyl-10-deacetylbaecatin III with excess acetyl chloride, working in a basic organic solvent such as pyridine, at a temperature in the region of 0°C. Generally, 7-trialkylsilyloxybaecatin III of formula (I) is obtained with a yield of 85% from 7-triethylsilylbaecatin III.

Thus, according to the known process, a

7-trialkylsilylbaccatin III is obtained with a yield in the region of 72%.

It has now been found, and this forms the subject of the present invention, that the product of
5 general formula (I) may be obtained with better yields by carrying out the silylation and the acetylation without isolation of the intermediate 7-trialkylsilyl-10-deacetylbaccatin III.

According to the invention, 10-
10 deacetylbaccatin III, dissolved in a basic organic solvent chosen from pyridine and pyridines substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, is treated with a silylating agent of general formula (III) at a temperature between 0 and
15 15°C, and then with acetic anhydride at a temperature in the region of 20°C.

The use of the process according to the invention requires the use of a much smaller excess of silylating agent than in the known process. Generally,
20 from 1.5 to 2.5 mol of silylating agent are used per mole of 10-deacetylbaccatin III used.

Generally, 5 to 7 mol of acetic anhydride are used per mole of 10-deacetylbaccatin III used.

The 7-trialkylsilylbaccatin III may be
25 isolated after precipitation in water and crystallization, from its solution in an aliphatic ester such as ethyl acetate, using an ether such as isopropyl ether. Generally, the yield is in the region

of 80% from the 10-deacetylbaaccatin III used.

The 7-trialkylsilylbaaccatin III, obtained according to the process of the present invention, may be used, after isolation or dissolved in an aliphatic ester such as ethyl acetate, in order to prepare paclitaxel or derivatives thereof according to known processes as described, for example, in European Patent EP-0,336,840 or in International Application WO 92/09589.

The example which follows illustrates the use of the process according to the invention.

EXAMPLE

To a solution of 293.9 g of 10-deacetylbaaccatin III in 2.7 litres of pyridine are added, over 1 hour 20 minutes, 182 g of triethylsilyl chloride. The solution obtained is stirred for 40 hours at 5°C. 360 g of acetic anhydride are then added while maintaining the temperature at 5°C. The suspension obtained is stirred for 48 hours at 20°C and is then poured onto 40 litres of ice-cold water. The precipitate obtained is separated by filtration and then washed with 8 times 2 litres of water and finally dissolved in 3 litres of ethyl acetate. The organic phase is dried over magnesium sulphate. After filtration and concentration under reduced pressure, the product obtained is crystallized from isopropyl ether. 7-triethylsilylbaaccatin III is thus obtained

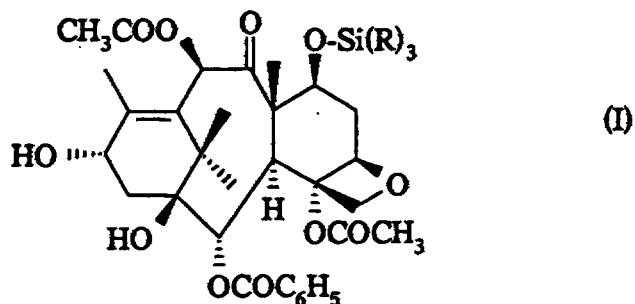
with a yield of 77%, the characteristics of which product are as follows:

- melting point: 254°C

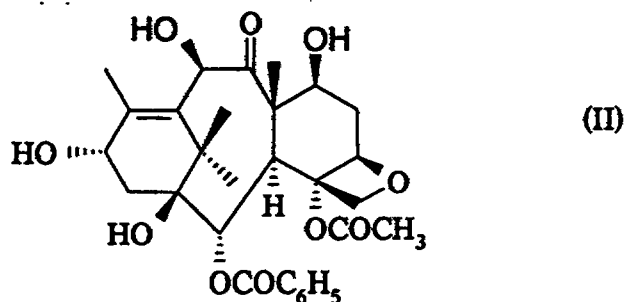
- proton nuclear magnetic resonance spectrum : (400
 5 MHz; CDCl_3 , δ in ppm) : 0.58 (mt, 6H : CH_2 ethyl) ; 0.92
 (t, $J = 7.5$ Hz, 9H : CH_3 ethyl) ; 1.02 (s, 3H : CH_3) ;
 1.18 (s, 3H : CH_3) ; 1.68 (s, 3H : CH_3) ; 1.75 (broad s,
 1H : OH at 1) ; 1.87 and 2.53 (2 mt, 1H each : CH_2 at
 6) ; 2.18 (s, 6H : CH_3 and COCH_3) ; 2.27 (mt, 2H : CH_2 at
 10 14) ; 2.28 (s, 3H : COCH_3) ; 2.47 (broad s, 1H : OH at
 13) ; 3.88 (d, $J = 7$ Hz, 1H : H3) ; 4.13 and 4.30 (2d,
 $J = 8.5$ Hz, 1H each : CH_2 at 20) ; 4.50 (dd, $J = 11$ and
 7 Hz, 1H : H at 7) ; 4.81 (mt, 1H : H at 13) ; 4.95
 (broad d, $J = 10$ Hz, 1H : H at 5) ; 5.63 (d, $J = 7$ Hz,
 15 1H : H2) ; 6.46 (s, 1H : H at 10) ; 7.46 (t, $J = 8.5$ Hz,
 2H : $-\text{OCOC}_6\text{H}_5$ meta H) ; 7.60 (t, $J = 8.5$ Hz, 1H : -
 OCOC_6H_5 para H) ; 8.10 (d, $J = 8.5$ Hz, 2H : $-\text{OCOC}_6\text{H}_5$
 ortho H).

CLAIMS

1. Process for the preparation of 7-trialkylsilylbaccatin III of general formula:



in which the symbols R, which may be identical or
5 different, represent straight or branched alkyl
radicals containing 1 to 4 carbon atoms which are
optionally substituted with a phenyl radical,
characterized in that 10-deacetylbaecatin III of
formula:



10 is treated with a silylating agent of general formula:



in which R is defined as above, then with acetic anhydride without isolating the intermediate 7-trialkylsilyl-10-deacetylbaccatin III.

15 2. Process according to claim 1,

characterized in that the process is performed in a basic organic solvent.

3. Process according to claim 2, characterized in that the basic organic solvent is
5 chosen from pyridine and pyridines substituted with one or more alkyl radicals containing 1 to 4 carbon atoms.

4. Process according to claim 2, characterized in that the basic organic solvent is pyridine.

10 5. Process according to either of claims 1 and 2, characterized in that from 1.5 to 2.5 mol of silylating agent are used per mol of 10-deacetylbaecatin III used.

15 6. Process according to either of claims 1 and 2, characterized in that from 5 to 7 mol of acetic anhydride are used per mole of 10-deacetylbaecatin III used.

20 7. Process according to either of claims 1 and 2, characterized in that the treatment with the silylating agent is carried out at a temperature between 0 and 15°C.

25 8. Process according to either of claims 1 and 2, characterized in that the treatment with acetic anhydride is carried out at a temperature in the region of 20°C.

9. Process according to one of claims 1 to 8 for the preparation of a 7-trialkylsilylbaecatin III of general formula (I) in which each of the symbols R

represents an alkyl radical containing 1 to 3 carbon atoms.

10. Process according to one of claims 1 to 8 for the preparation of a 7-trialkylsilylbaccatin III of general formula (I) in which each of the symbols R represents an ethyl radical.

PCT WORLD ORGANISATION FOR INTELLECTUAL PROPERTY
International Office
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International patent classification⁶ : C07F 7/18	A1	(11) International publication number: WO 95/26967 (43) International publication date: 12 October 1995 (12.10.95)
(21) International application number: PCT/FR95/00419 (22) International filing date: 3 April 1995 (03.04.95) (30) Data relating to the priority: 94/03,979 5 April 1994 (05.04.94) FR (71) Applicant (for all designated States except US): RHONE-POULENC RORER S.A. [FR/FR]; 20, avenue Raymond-Aron, F-92160 Antony (FR). (72) Inventors; and (75) Inventors/Applicants (US only): Jean-Pierre BASTART [FR/FR]; 12, rue des Bergères, F-77500 Lesigny (FR). Jean-Pierre LECONTE [FR/FR]; 17, avenue Galliéni, F-91800 Brundy (FR). (74) Representative: Jacques PILARD; Rhône-Poulenc Rorer S.A., Patents Directorate, 20, avenue Raymond- Aron, F-92165 Antony (FR).	(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN, European Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, GA, GN, ML, MR, NE, SN, TD, TG) ARIPO Patent (KE, MW, SD, SZ, UG). Published With the International Search Report.	
(54) Title: PROCESS FOR PREPARING 7-TRIALKYSILYL BACCATIN III (54) Titre: PROCEDE DE PREPARATION DE TRIALCOYLSILYL-7 BACCATINE III (57) Abstract Process for preparing 7-trialkylsilyl baccatin III from 10-deacetyl baccatin III. (57) Abrégé Procédé de préparation de la trialcoylsilyl-7 baccatine III à partir de la désacétyl-10 baccatine III.		