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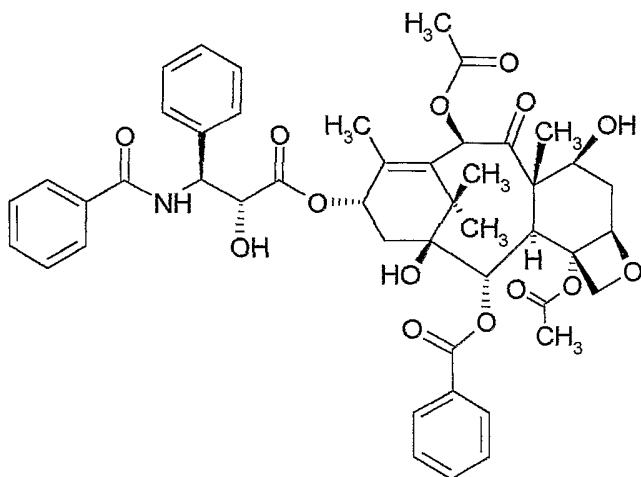
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- (71) Applicant (for all designated States except US):
AGROPHARM S.A. [PL/PL]; ul. Staroscianska 33,
PL-95-080 Tuszyn k/kodz (PL).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): **KOLESINSKA, Beata** [PL/PL]; Niesiolowice 41, PL-23-240 Jozefow n. Wisla (PL). **KAMINSKI, J., Zbigniew** [PL/PL]; Al. Wyszynskiego 96 m 1, PL-94-050 Lodz (PL). **KAMINSKA, E., Janina** [PL/PL]; Al. Wyszynskiego 96 m 1, PL-94-050 Lodz (PL).
- (74) Agent: **PADEE, Grazyna**; ul. Noakowskiego 18/20, PL-00-668 Warszawa (PL).
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(54) Title: THE METHOD FOR PRODUCTION OF SEMI-FINISHED PRODUCTS USEFUL IN SYNTHESIS OF PACLITAXEL



(2)

(57) Abstract: The method for production of the semi-finished products useful in synthesis of Paclitaxel with the generalized formula (2), characterized in that phenyl isoserine derivatives, or mixtures of their epimerides with various configurations on the carbon 2' or their salts, are treated with triazine type condensing agent, possible in the presence of tertiary amine, in medium of anhydrous organic solvent, and the triazine esters produced are treated with Baccatin III, in medium of anhydrous organic solvent, possible in the presence of a catalyst.

The method for production of semi-finished products useful in synthesis of Paclitaxel

The matter of the invention is the method for production of semi-finished products useful in synthesis of Paclitaxel.

Paclitaxel (formula 1) is a natural compound showing wide spectrum of antitumor activity, originally isolated from bark of yew *Taxus brevifolia* [Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggen, P.; McPhail, A.T., *J. Am. Chem. Soc.*, **93**, 2325, (1971)] occurring also in other natural products. Considering low concentrations and difficult regeneration of the natural resources, process of isolation Paclitaxel from plants is of marginal importance. The most effective procedure for production of Paclitaxel is *semi-synthesis*, based on suitable secured Baccatin III and also secured phenyl isoserine. Baccatin III (formula 3, where $R_2=H$) is a heterocyclic compound, characterized by condensed ring arrangement in the [9.3.1.0]^{3,8} pentadecane structure, configured identically as a fragment of Paclitaxel. Baccatin III is obtained from deacetobaccatin II, which occurs in dried needles of yew *Taxus baccata* concentration approximating to 1 g in 1 kg of the material. Isolation of the substance is an economically sound process, and the resources (needles and shoots) are quite renewable within every one season of vegetation.

All the reported methods for *semi-synthesis* of Paclitaxel are based on the concept of formation of an ester type bond between suitable secured Baccatin III derivative and also secured phenyl isoserine derivatives. However, it should be pointed out, that both the esterification procedure and the product of esterification processing technique depend upon strategy of synthesis and on the type of the protective groups used.

Kingston, D.G.I.; Chaudhary, A.G. Gunatilaka, A.A.L.; Middleton, M.L. in their paper published in *Tetrahedron Lett.*, **35**, 4483-4484 (1994) and in the patent specification WO 97/00870 presented application of dicyclohexylcarboimide (DDC) in presence of 4-(1-pyrrolidin)pyridine for bounding of 7-(triethylsilyl)baccatin [formula 3; $R_1=Si(C_2H_5)_3$] to 2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic acid, what after removal of the protective groups, provides Paclitaxel at the overall yield of more than 70%.

Similar solution, based on dicyclohexylcarboimide (DCC) in presence of 4-(N,N-dimethylamino)pyridine (DMAP), described by Balogu, E. and Kingston, D.G.I in their paper published in *J. Nat. Prod.* **62**, 1068-1071, (1999) proved to be considerable less effective, because product of condensation yielded 30% yield, only. Moreover, N,N'-dicyclohexylcarboimide was used for acylation of the 7-protected Baccatin derivatives with oxazolidynes and with other phenyl isoserine derivatives.

Drawbacks of all the N,N'- dicyclohexylcarboimide based procedures are difficulties encountered in removal of N,N'- dicyclohexylcarbamide, undesirable by-product, from the reaction medium. N,N'- dicyclohexylcarbamide is a troublesome impurity of the condensation product because it is sparingly soluble in most of organic solvents, therefore its effective separation from also sparingly soluble Paclitaxel derivatives is difficult. It complicates the process of isolation of intermediates from the final product and reduces effectiveness of utilization of the phenyl isoserine and Baccatin components. Another awkward drawback of DCC is its ability for developing of allergy, manifesting by pathological changes of epidermis. Relatively high vapor pressure of DCC at room temperature results in development of allergic symptoms even in persons, which have no direct contact with the compound.

There are known also other solutions, in which instead of N,N'-dicyclohexylcarboimide other condensing agents are used. Gennori, C.; Garcano, M.; Dughi, M.; Mongelli, N.; Vanatti, E.; Wulpetti, A. in their paper published in *J. Org. Chem.* **62**, 4746-4755, (1997), described condensation of 7-(triethylsilylo)baccatin with thiophenyl ester of 2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic acid in presence of bis-trimethylsilyloamidolite (LHMDS). It yielded 89% of semi-finished product, structure of that was identical to that obtained by Kingston, D. G. et all. with use of N,N'-dicyclohexylcarboimide, as described in *Tetrahedron Lett.*, **35**, 4483-4484 (1994).

Mukaiyama, T. et all. condensed 7-triethylsilylobaccatin with phenylisoserine derivative [formula 4c, where $R_3=H$, $R_4=p-C_6H_4OCH_3$] in presence of di-(2-pyridil)-thionic carbonate reaching yield of 93%, as published in *Chem. Europ. J.*

Whereas Shiina, I. et all. described in *Chem. Lett.*, **1**, 204 (1998) that condensation of protected Baccatin and phenylisoserine derivative [formula 4b, where $R_2=CH_2C_6H_5$] in presence of di-(2-pyridil)-thionic carbonate gives yields 66%, only. Swindell, C. S. et all. in *J. Med. Chem.*, **34**, 1176-1184 (1991) and Greene, A. E. et all. in *J. Am. Chem. Soc.* **110**, 5917 (1998) also described condensation of phenylisoserine derivative with protected Baccatin in presence of dipyridil carbonate and 4-(N,N-dimethylamino)pyridine but the yields reported were moderate.

Patent specification US 6,150,537 provides results of application of acyl chlorides and ketones, obtained from phenylisoserine derivatives, for acylation of the hydroxy group in Baccatin. Considerable drawback of the solution is difficult synthesis of the mentioned phenylisoserine derivatives and the risk of epimerization in course of synthesis of such reactive compounds.

Holton et al. (*J.Am.Chem.Soc.*, **116**, 1599-1600, (1994), WO93/06079) in many examples documented suitability of 4-phenyl-3-hydroxyazetydinone-2 derivatives (β -laktam derivatives) for acylation of Baccatin (usually protected in the 7. position with the triethylsilyl group). Application of the β -laktam derivatives provides the possibility for highly effective acylation, however preparation of these derivatives is a very complex and multistage process.

There are also known applications of phenylisoserine derivatives transformed into a six-membered oxazine ring [US Pat. No 5,015,744, and Beckwermist et al. in *J. Org. Chem.*, **61**, 9038-9040 (1996)], however the overall yield of the process is not satisfactory.

According to the invention, the method for bonding of phenylisoserine and baccatine components consists of utilization of another condensing agent, what effectively eliminates the troubles usually encountered when dicyclohexylcarbodiimide was used, acyclic chlorides, ketenes, thiol esters, di-(2-pyridyl)carbonate, di-(2-pyridyl)thiocarbonate, etc.

The method for production of semi-finished products useful in synthesis of Paclitaxel, with the generalized formula 2, where R_1 denotes a group with formula 7, or a group with formula 8, or a group with formula 9, or a group with formula 10, R_2 denotes hydrogen, alkylsilyl group or substituted alkylsilyl group, arylsilyl group or substituted arylsilyl group, alkylarylsilyl group or substituted alkylarylsilyl group, alkoxycarbonyl group or substituted alkoxycarbonyl group, alkoxymethyl group or substituted alkoxymethyl group, R_3 and R_4 denote hydrogen, alkyl group or substituted alkyl group, aryl group or substituted aryl group, and X denotes C=O, C=S, S=O, SO₂, (C=O)₂, P(aryl)₃, P-N(alkyl)₂, (P=O)-N(alkyl)₂, (P=S)-N(alkyl)₂, by reaction of Baccatin III derivatives and phenylisoserine derivatives, consists in reaction of phenylisoserine derivatives, with the generalized formulas 4a-d, where R_2 , R_3 , R_4 and X have above specified meanings, or a mixture of their epimers having various configurations in the carbon 2', or their salts, with triazin based condensing agent with the generalized formula 5, where R_5 and R_6 denote chlorine, alkoxy group, substituted alkoxy group, aryloxy group or substituted aryloxy group, whereas R_7 denotes fluorine, chlorine or a quaternary ammonia group, possible in the presence of a tertiary amine group, in anhydrous organic solvent medium, followed

by reaction of such obtained triazine esters of phenylisoserine, with the generalized formulas 6a-d, where R_2 , R_3 , R_4 and X have above specified meanings, with Baccatin with the generalized formula 3, where R_2 denotes hydrogen or a group which protects functional hydroxy group in the position 7., in anhydrous organic solvent, if need be in presence of a catalyst.

Beneficially, phenyl isoserine derivatives are used, in which R_3 and R_4 denote hydrogen, methyl group, phenyl group, metoxyphenyl group or dimetoxi phenyl group.

Beneficially, the hydroxyl group in the 7. position of Baccatin III is protected by alkylsilol group or substituted alkylsilol group, arylsilol group or substituted arylsilol group, alkylarylsilol group or substituted alkylarylsilol group, alkoxycarbonyl group or substituted alkoxycarbonyl group, alkoxymethyl group or substituted alkoxymethyl group.

Beneficially, salts of phenyl isoserine are salts of metals, particularly of alkali metals or salts of tertiary amines, beneficially of N-methylmorpholine, N,N-dimethylaminopyridyne or 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU).

Beneficially, as the triazine based condensing reagent there is used 2-chloro-4,6-dimethoxy-1,3,5-triazine or quarternary triazinyl ammonium salts, obtained by reaction of 2-chloro-4,6-dimethoxy-1,3,5-triazine with ternary amines.

Beneficially, the tertiary amine is N-methylmorpholine, tetramethylguanidyne, 1,4-dimethylpiperazyne, N-methylpyrolidyne, N,N'-tetramethylethylodiamine, N-methylpiperidine, pyridine, pyridine derivatives substitutes in the 4. Position of the pyridine ring, 1,8-diazabicyclo[5.4.0.]undec-7-en.

Beneficially, the solvent is an a-proton solvent, particularly aromatic hydrocarbons, chlorinated hydrocarbons, ethers, acid amides, nitriles of acids. Particularly beneficial is application of toluene, dichlormethane, dichlorethane, tetrahydrofurane, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide and N,N',N'-hexamethylamide of phosphoric acid, acetonitrile.

Beneficially, the reaction of acylation of Baccatin III proceeds in presence of Lewis-type acid and particularly in presence of anhydrous magnesium bromide.

Beneficially, reaction of acylation of Baccatin III is accomplished in presence of a base, particularly of tertiary amine, and the best in presence of 4-(N,N-dialkylamino)pyridine or DBU.

If the need be, triazine esters of phenyl isoserine may be removed from the reaction medium, before reaction with Baccatin III.

Next, the semi-finished products obtained with the method of invention are transformed into Paclitaxel with known methods, selected accordingly to the nature of the protective group used in reaction of Baccatin and phenyl isoserine. These known methods for

transformation of the semi-finished products obtained with the method of invention into Paclitaxel are described e.g. in the publication „Protective Group in Organic Synthesis”, ed.2, J. Wiley and Son, 1991.

Triazine type condensing reagents are easily available, of low toxicity and not develop of allergy. They activate the carboxylic function in mild conditions, and process of acylation of the carboxyl function may be accelerated by introduction of suitable catalysts, if required. Both the triazine type condensing reagents, triazine esters and all by-products formed are weak bases in character and after the end of the process, may be readily removed by washing out with diluted acid solutions. The fact makes purification of Paclitaxel and its derivatives, easier and is conducive to high yield of the process.

Very reactive triazine esters may be isolated from the mixture but more convenient is synthesis directly before, or in course of coupling of the phenyl isoserine and the Baccatin components. Such procedure is advantageous, because most of the phenyl isoserine derivatives suitable for *semi*-synthesis of Paclitaxel and the triazine condensation agents are stable and may be easily stored, without any decomposition trace until will be used for coupling with suitable protected Baccatin III.

The method of invention is illustrated by following practicable examples.

1. Example

Solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (7.71 g, 44 mmol) in 100 ml THF was mixed with N-methylmorpholine (4.84 ml, 44 mmol) for 30 minutes at temperature of 0-5°C. Then, there was added mixture of diastereomers of the **4b** acid, where R₃=H and R₄=3,4-dimethoxyphenyl (19.05 g, 44 mmol) and further mixed for 4 hours at temperature of 0-5°C, followed by mixing for 8 hours at room temperature. Precipitate was filtered off and to the filtrate (without separation of triazine ester) protected Baccatin III of the 3. formula, where R₂=Si(C₂H₅)₃ (28.1g, 40 mmol), DMAP (0.24 g, 2 mmol) MgBr₂ (0.36 g, 2 mmol) and triethylamine (3.84 g, 38 mmol) were added. After reaction was completed, solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed in turn with: H₂O, 1M KHSO₄, H₂O, 1M NaHCO₃, H₂O by 20 ml each. TLC: (acetone : benzene 1:4) R_f=0.75 and 0.8. The process yielded 44.6 g (quantitative yield) of the product with the formula **2**, where R₁ is defined with the formula **8**, R₂ is the triethylsilyl group, R₃=H, and R₄=3,4-dimethoxyphenyl. Raw product of condensation was dissolved in the mixture methanol/THF (80 ml/450 ml, respectively) and for 40 minutes treated with concentrated hydrochloric acid (30 ml). The mixture was poured into ice water and ethyl acetate mix, the layers separated, then the water phase was extracted with ethyl acetate. The organic phases were connected together and washed with saturated water solution of sodium

bicarbonate, dried with magnesium sulfate and concentrated under reduced pressure until dry. Dry residue was chromatographed in a column filled with silica gel. Finally, the product was eluted with the mixture of ethyl acetate/hexane 1:1 (v/v). It gave 28.5 g Paclitaxel with melting point of 221-223°C. The yield amounted to 82%.

$[\alpha]_D^{20} = -49$ (c=0.45, MeOH).

$^1\text{H-NMR}$: (250 MHz, CDCl_3): δ =1.14 (s, 3H); 1.24 (s, 3H); 1.69 (s, 3H); 1.79 (s, 3H), 1.82 (s, 1H); 1.88 (m, 1H); 2.24 (s, 3H), 2.25-2.40 (m, 2H); 2.39 (s, 3H); 2.49 (d, J=4.0 Hz, 1H), 2.50-2.55 (m, 1H); 3.59 (d, J=5.0 Hz, 1H); 4.17 (d, J=9.0 Hz, 1H); 4.29 (d, J=9.0 Hz, 1H); 4.37-4.40 (m, 1H); 4.75-4.79 (m, 1H); 4.95 (m, 1H); 5.67 (d, J=7.0 Hz, 1H); 5.77-5.80 (m, 1H); 6.22 (t, J=8.0 Hz, 1H); 6.25 (s, 1H); 7.05 (d, J=9.5 Hz, 1H); 7.31-7.55 (m, 7H); 7.61-7.65 (m, 1H); 7.71-7.75 (m, 2H); 8.09-8.15 (m, 2H) [ppm]

$^{13}\text{C-NMR}$: (250 MHz, CDCl_3): δ =9.4; 15.0; 20.8; 21.7; 22.6; 26.7; 35.5; 35.5; 43.2; 45.5; 55.1; 58.7; 72.2; 72.4; 73.3; 75.0; 75.5; 76.6; 79.1; 81.2; 84.5; 127.2; 127.4; 128.5; 138.8; 128.8; 129.1; 129.2; 130.3; 132.1; 133.1; 133.7; 133.8; 133.9; 142.0; 167.1; 167.1; 170.7; 171.5; 172.9; 203.7 [ppm].

IR: 1240, 1550, 166,0; 2970; 3480 [cm^{-1}].

FAB-MS: 854 [$\text{MH}]^+$; 794 [$\text{MH-AcOH}]^+$, 776 [$\text{M-AcOH-H}_2\text{O}]^+$.

CI(isobutane) MS: 854 [$\text{MH}]^+$; 836 [$\text{MH-H}_2\text{O}$]; 818 [$\text{MH-2H}_2\text{O}]^+$.

2. Example

N-(4,6-dimethoxy-1,3,5-triazin-2-yl)-N-methylmorpholine chloride (0.278 g, 1 mmole), cooled down to temperature of 0-5°C in 5 ml chloroform was connected with mixture of epimerides of the **4b** acid, where $\text{R}_3=\text{H}$ and $\text{R}_4=3,4\text{-dimethoxyphenyl}$ (0.433 g, 1 mmole) and mixed for 12 hours. N-methylmorpholine chloride was washed off with ice water, and organic phase was dried with MgSO_4 , the drying agent was filtered off and the filtrate was evaporated under reduced pressure until dry. It gave respective triazine ester of the formula **6b**, where $\text{R}_3=\text{H}$, $\text{R}_4=3,4\text{-dimethoxyphenyl}$, and $\text{R}_5=\text{R}_6=\text{OCH}_3$, with the quantitative yield.

TLC: eluent CHCl_3 , $\text{R}_f=0.55$

$^1\text{H-NMR}$ (250 MHz, CDCl_3): δ = 3.54 (s, 6H); 3.80 (s, 3H); 3.85 (s, 3H); 5.34 (d, J=, 1H); 6.19 (d, J=, 1H), 6.74 (bs, 1H); 7.07 (bs, 1H); 7.14 (bs, 1H); 7.21 (bs, 1H); 7.28-7.80 (m, 10H) [ppm]

IR (CCl_4): 1750 [cm^{-1}]

The triazine ester was used for reaction with protected Bacctain of the generalized formula **3**, where $\text{R}_2=\text{Si}(\text{C}_2\text{H}_5)_3$ (28.1g, 40 mmoles), DMAP (6 μg , 0.05 mmole) MgBr_2 (9 μg , 0.05 mmole) and triethylamine (96 μg , 0.95 mmole). After the reaction was finished, solvent was removed by evaporation under reduced pressure whereas the residue was

dissolved in ethyl acetate and washed in turn with: H₂O, 1M KHSO₄, H₂O, 1M NaHCO₃, H₂O by 20 ml each. TLC: (acetone : benzene 1:4) R_f=0.75, 0.8. It gave 1.1 g (yield 95%) of the product with the formula **2**, where R₁ is defined with the formula **8**, R₂= Si(C₂H₅)₃, R₃=H, and R₄=3,4-dimethoxyphenyl.

¹H-NMR: (250 MHz, CDCl₃): δ=0.51 (q, J=8.0 Hz, 6H); 1.23 (s, 3H); 1.22 (t, J=8.0 Hz, 9H); 1.35 (s, 3H); 1.85 (s, 1H); 1.95 (s, 3H); 2.08 (s, 3H); 2.14 (s, 3H); 2.16-2.28 (m, 1H); 2.41-2.45 (m, 1H), 2.55-2.58 (m, 1H); 2.59 (s, 3H); 2.65-2.85 (m, 1H); 3.28 (s, 3H); 3.38 (s, 3H); 4.25 (d, J=7.0 Hz, 1H); 4.41 (d, J=9.0 Hz, 1H); 4.48 (d, J=9.0 Hz, 1H); 4.85 (s, 1H); 4.92-4.96 (m, 1H); 5.07 (d, J=8.5Hz, 1H); 6.02 (s, 1H); 6.15 (d, J= 7.5Hz, 1H); 6.62-6.68 (m, 1H); 6.85-6.95 (m, 3H), 6.98-7.08 (m, 2H); 7.12-7.38 (m, 7H); 7.39-7.45 (m, 2H); 7.51 (s, 1H); 7.61 (d, J=7.5Hz, 1H); 7.77-7.87 (m, 2H); 8.28-8.35 (m, 2H) [ppm]

3. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.175 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C. Then, easily migrated epimeride **4b**, where R₃=H, and R₄=3,4-dimethoxyphenyl (0.433 g, 1 mmol) was added and mixed for 12 hours. N-methylmorpholine chloride was filtered off, and filtrate was evaporated until dry under reduced pressure. It gave respective triazine ester of the formula **6b**, where R₃=H, R₄=3,4-dimethoxyphenyl, and R₅=R₆=OCH₃, with the quantitative yield.

TLC: eluent CHCl₃, R_f=0,7.

¹H-NMR (250 MHz, CDCl₃): δ= 3.52 (s, 6H); 3.80 (s, 3H); 3.85 (s, 3H); 5.34 (d, J=, 1H); 6.19 (d, J=, 1H), 6.74 (bs, 1H); 7.07 (bs, 1H); 7.11 (bs, 1H); 7.21 (bs, 1H); 7.28-7.80 (m, 10H) [ppm]

IR (CCl₄): 1750 [cm⁻¹]

The triazine ester, in the presence of 4-(pyrrolidin)pyridine, was coupled with protected Bacctain of the generalized formula **3**, where R₂=Si(C₂H₅)₃. After the reaction was finished, raw product was extracted as described in the 1. Example. After removal of protective groups and chromatography it gave Paclitaxel with melting point of 220-223°C and chromatographic and spectral characteristics identical to those described in the 1. Example.

4. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.175 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C. Then, hardly migrating epimeride **4b**, where R₃=H, and R₄=3,4-dimethoxyphenyl (0.433 g, 1 mmol) was added and mixed for 12 hours. N-methylmorpholine chloride was filtered off, and filtrate was evaporated until dry under reduced pressure. It gave

respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4\text{-dimethoxyphenyl}$, and $R_5=R_6=OCH_3$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.6$

$^1H\text{-NMR}$ (250 MHz, $CDCl_3$): $\delta= 3.56$ (s, 6H); 3.80 (s, 3H); 3.85 (s, 3H); 5.34 (d, $J=$, 1H); 6.19 (d, $J=$, 1H), 6.74 (bs, 1H); 7.07 (bs, 1H); 7.14 (bs, 1H); 7.21 (bs, 1H); 7.28-7.80 (m, 10H) [ppm]

IR (CCl_4): 1740 [cm^{-1}]

The triazine ester, in the presence of magnesium bromide and 4-(pyrolidin)pyridine, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. After the reaction was finished, raw product was extracted as described in the 1. Example. After removal of protective groups and chromatography it gave Paclitaxel with melting point of 220-223°C and chromatographic and spectral characteristics identical to those described in the 1. Example.

5. Example

Solution of 2-chlor-4,6-diphenoxy-1,3,5-triazine (CDPhT) (0.3 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to obtain N-(4,6- diphenoxy -1,3,5-triazine-2-yl)-N- methylmorpholine chloride. Then, mixture of epimerides of acids **4b**, where $R_3=H$, and $R_4=3,4\text{-dimethoxyphenyl}$ (0.433 g, 1 mmol) was added and mixed for 12 hours. After N-methylmorpholine chloride was filtered off, and filtrate was evaporated it gave respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4\text{-dimethoxyphenyl}$, and $R_5=R_6=OCH_3$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.45$,

$^1H\text{-NMR}$ (250 MHz, $CDCl_3$): $\delta=3.80$ (s, 3H); 3.85 (s, 3H); 5.34 (d, $J=$, 1H); 6.19 (d, $J=$, 1H), 6.74 (bs, 1H); 7.07 (bs, 1H); 7.09 (bs, 1H); 7.10 (bs, 1H); 7.11-7.76 (m, 20H) [ppm]

IR (KBr): 1770 [cm^{-1}]

The triazine ester, in the presence of magnesium bromide and 4-(pyrolidin)pyridine, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 2. Example.

6. Example

Solution of 2,4-dichlor-1,3,5-triazine (DCMT) (0.09 g, 0.5 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to form respective quaternary triazinammonium salt. Then, mixture of epimerides **4b**, where $R_3=H$, and $R_4=3,4\text{-dimethoxyphenyl}$ (0.433 g, 1 mmol) was added and mixed for 12 hours, first at temperature of 0-5°C next at room temperature. N-methylmorpholine

hydrochloride was filtered off, and solvent from filtrate was evaporated. It gave respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4$ -dimethoxyphenyl, and $R_5=OCH_3$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.45$

1H -NMR ($CDCl_3$): $\delta=3.63$ (s, 3H); 3.80 (s, 3H); 3.85 (s, 3H); 5.34 (d, J=, 1H); 6.19 (d, J=, 1H), 6.74 (bs, 1H); 7.07 (bs, 1H); 7.14 (bs, 1H); 7.21 (bs, 1H); 7.28-7.80 (m, 10H) [ppm]

IR (KBr): 1760 [cm^{-1}]

The triazine ester, in the presence of magnesium bromide, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 2. Example.

7. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.175 g, 1 mmole) in 5 ml acetonitrile was mixed with tetramethyloguanidyne (0.126 ml, 1 mmole) for 30 minutes at temperature of 0-5°C. Then, mixture of epimerides of acids **4b**, where $R_3=H$, and $R_4=3,4$ -dimethoxyphenyl (0.433 g, 1 mmol) was added and mixed for 12 hours. Tetramethyloguanidyne hydrochloride was washed off with ice water, filtrate was dried over $MgSO_4$, next the drying agent was filtered off and the residue was evaporated until dry under reduced pressure. It gave respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4$ -dimethoxyphenyl, and $R_5=R_6=OCH_3$, with the quantitative yield.

The triazine ester, in the presence of magnesium bromide, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 2. Example.

8. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.175 g, 1 mmole) in 5 ml toluene was mixed with 1,4-dimethylpiperazyne (0.135 ml, 1 mmole) for 30 minutes at temperature of 0-5°C. Then, mixture of epimerides of acids **4b**, where $R_3=H$, and $R_4=3,4$ -dimethoxyphenyl (0.433 g, 1 mmol) was added and mixed for 12 hours. 1,4-dimethylpiperazyne hydrochloride was filtered off, filtrate was evaporated until dry under reduced pressure. It gave respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4$ -dimethoxyphenyl, and $R_5=R_6=OCH_3$, with the quantitative yield.

The triazine ester, in the presence of 4-(N,N-dimethylamin)pyridyne, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 2. Example.

9. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.175 g, 1 mmole) in 5 ml DMF was mixed with N-methylpiperidine (0.104 ml, 1 mmole) for 30 minutes at temperature of

0-5°C. Then, mixture of epimerides of acids **4b**, where $R_3=H$, and $R_4=3,4$ -dimethoxyphenyl (0.433 g, 1 mmol) was added, mixed for 12 hours and evaporated until dry under reduced pressure. After washing off, respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4$ -dimethoxyphenyl, and $R_5=R_6=OCH_3$ was obtained with the quantitative yield. The triazine ester, in the presence of magnesium bromide and 4-(N,N-dimethylamin)pyridyne, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 2. Example.

10. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.175 g, 1 mmole) in 5 ml dichloroethane was mixed with N-methylpyrrolidyne (0.104 ml, 1 mmole) for 30 minutes at temperature of 0-5°C. Then, mixture of salts of epimerides of acids **4b**, where $R_3=H$, and $R_4=3,4$ -dimethoxyphenyl (0.455 g, 1 mmol) was added and mixed for 12 hours. After washing off and evaporation of solvent, respective triazine ester of the formula **6b**, where $R_3=H$, $R_4=3,4$ -dimethoxyphenyl, and $R_5=R_6=OCH_3$ was obtained with the quantitative yield.

The triazine ester, in the presence of magnesium bromide and 4-(N,N-dimethylamin)pyridyne, was coupled with protected Bacctain III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 2. Example.

11. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (0.175 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C, to form respective quaternary triazinilammonium salt. Then, phenyl isoserine of the formula **4b**, where $R_3=R_4=CH_3$ (0.325 g, 1 mmol) was added and mixed for 12 hours, first at temperature of 0-5°C, next at room temperature. N-methylmorpholine was filtered off and solvent was removed from the filtrate. It gave respective triazine ester of the formula **6b**, where $R_3=R_4=CH_3$, $R_5=R_6=OCH_3$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.50$

1H -NMR ($CDCl_3$): $\delta= 1.76$ (s, 3H); 1.79 (s, 3H); 3.76 (s, 6H); 5.20 (d, $J= 7.5$ Hz, 1H); 5.59, (d, $J= 7.5$ Hz, 1H); 7.43-7.56 (m, 8H); 7.70-7.43 (m, 2H) [ppm].

IR (KBr): 1790 [cm^{-1}]

The triazine ester was coupled with protected Bacctain III of generalized formula **3**, where $R_2=Si(C_2H_5)_3$, in the presence of magnesium bromide and diazobicycloundekane. It gave 0.945 g of the final product (93.8%) with the melting temperature of 171-173°C.

TLC: eluent (acetone:benzene 1:4), $R_f=0.85$

$^1\text{H-NMR}$ (CDCl_3): $\delta=0.55$ (q, $J=8.5$ Hz, 6H); 0.94 (t, $J=8.5$ Hz, 9H); 1.17 (s, 3H); 1.22 (s, 3H); 1.67 (s, 3H); 1.77 (s, 1H); 1.83-1.85 (m, 1H); 1.87 (s, 3H); 1.94 (s, 3H); 2.02 (s, 3H); 2.07 (s, 3H); 2.02-2.18 (m, 2H); 2.19 (s, 3H); 2.07-2.20 (m, 2H); 2.48-2.50 (m, 2H); 3.77 (d, $J=7.5$ Hz, 1H); 4.07 (d, $J=8.5$ Hz, 1H); 4.25 (d, $J=8.5$ Hz, 1H); 4.42-4.46 (m, 1H); 4.58 (d, $J=7.5$ Hz, 1H); 4.88-4.93 (m, 1H); 5.28 (d, $J=6.5$ Hz, 1H); 5.68 (d, $J=7.5$ Hz, 1H); 6.21-6.25 (m, 1H); 6.49 (s, 1H); 6.91-6.96 (m, 1H); 7.07-7.22 (m, 8H); 7.44-7.48 (m, 2H); 7.61-7.65 (m, 1H); 8.02 (d, $J=7.5$ Hz, 2H) [ppm]

The product of condensation was treated with formic acid in THF, and the final product was chromatographically purified on silica gel with the system of hexane: ethyl acetate 2:1. It gave 0.621 g (yield 76%) of a product spectroscopically and chromatographically identical to Paclitaxel.

12. Example

Solution of 2-chlor-4,6-diphenoxy-1,3,5-triazine (CDPhT) (0.3 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to obtain N-(4,6-diphenoxy-1,3,5-triazine-2-yl)-N-methylmorpholine chloride. Then, phenyl isoserine derivative with the formula **4b**, where $R_3=R_4=\text{CH}_3$ (0.325 g, 1 mmol) was added and mixed for 12 hours. After N-methylmorpholine hydrochloride was filtered off, and solvent was evaporated it gave respective triazine ester of the formula **6b**, where $R_3=R_4=\text{CH}_3$, and $R_5=R_6=\text{OC}_6\text{H}_5$, with the quantitative yield.

TLC: eluent CHCl_3 , $R_f=0.65$

$^1\text{H-NMR}$ (CDCl_3): $\delta=1.76$ (s, 3H); 1.79 (s, 3H); 5.19 (d, $J=8.0$ Hz, 1H); 5.27 (d, $J=8.0$ Hz, 1H); 7.19-7.22 (m, 2H); 7.40-7.74 (m, 18 H) ppm]

IR (KBr): 1780 [cm^{-1}]

The triazine ester, in the presence of magnesium bromide and pyrrolidinopyridine, was coupled with protected Baccatin III of the generalized formula **3**, where $R_2=\text{Si}(\text{C}_2\text{H}_5)_3$. The product was chromatographically and spectrally identical to that described in the 11. Example.

13. Example

Solution of 2,4-dichlor-1,3,5-triazine (DCMT) (0.09 g, 0.5 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to form respective quaternary triazinammonium salt. Then, phenyl isoserine derivative with the formula **4b**, where $R_3=R_4=\text{CH}_3$ (0.325 g, 1 mmol) was added and mixed for 12 hours, first at temperature of 0-5°C next at room temperature. N-methylmorpholine hydrochloride

was filtered off, and solvent from filtrate was evaporated. It gave respective triazine ester of the formula **6b**, where $R_3 = R_4 = \text{CH}_3$, and $R_5 = \text{OCH}_3$, with the quantitative yield.

TLC: eluent CHCl_3 , $R_f = 0.60$

$^1\text{H-NMR}$ (CDCl_3): $\delta = 1.76$ (s, 6H); 1.79 (s, 6H); 3.76 (s, 3H); 5.27 (d, $J = 7.5$ Hz, 2H); 5.49, (d, $J = 7.5$ Hz, 2H); 7.20-7.22 (m, 2H); 7.43-7.56 (m, 14H); 7.43-7.70 (m, 4H) [ppm]

IR (KBr): 1800 [cm^{-1}]

The triazine ester, in the presence of pyrrolidinopyridine, was coupled with protected Baccatin III of the generalized formula **3**, where $R_2 = \text{Si}(\text{C}_2\text{H}_5)_3$. The product was chromatographically and spectrally identical to that described in the 11. Example.

14. Example

Solution of 2-chlor-4,6-dimethoxy-1,3,5-triazine (0.175 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C, to form respective quaternary triazinilammonium salt. Then, phenyl isoserine of the formula **4c** (0.267 g, 1 mmol) was added and mixed for 12 hours, first at temperature of 0-5°C, next at room temperature. N-methylmorpholine hydrochloride was filtered off and solvent was removed from the filtrate. It gave respective triazine ester of the formula **6c**, where $R_5 = R_6 = \text{OCH}_3$, with the quantitative yield.

TLC: eluent CHCl_3 , $R_f = 0.50$

$^1\text{H-NMR}$ (CDCl_3): $\delta = 3.76$ (s, 6H); 5.31 (d, $J = 7.5$ Hz, 1H); 5.56 (d, $J = 7.5$ Hz, 1H); 7.35-7.48 (m, 6H); 7.75-7.77 (m, 2H); 8.04 (d, $J = 8.0$ Hz, 2H) [ppm]

IR (KBr): 1785 [cm^{-1}]

The triazine ester, in the presence of DMAP, was coupled with protected Baccatin III of the generalized formula **3**, where $R_2 = \text{Si}(\text{C}_2\text{H}_5)_3$. It gave 0.885 g of the final product (yield 91.5%) with the formula **2**, where R_1 is defined by the formula **9**, $R_2 = \text{Si}(\text{C}_2\text{H}_5)_3$.

TLC: eluent (acetone:benzene 1:4), $R_f = 0.75$

$^1\text{H-NMR}$ (CDCl_3): $\delta = 0.57$ (m, 6H); 0.95 (t, $J = 8.0$ Hz, 9H); 1.21 (s, 3H); 1.23 (s, 3H); 1.67 (s, 3H); 1.75 (s, 1H); 1.86-1.89 (m, 1H); 1.99 (s, 3H); 2.08 (s, 3H); 2.17 (s, 3H); 2.23-2.26 (m, 1H); 2.35-2.37 (m, 1H); 2.54-2.57 (m, 1H); 3.84 (d, $J = 7.5$ Hz, 1H); 4.16 (d, $J = 8.5$ Hz, 1H); 4.31 (d, $J = 8.5$ Hz, 1H); 4.47-4.50 (m, 1H); 4.93-4.96 (m, 2H); 5.60 (d, $J = 6.5$ Hz, 1H); 5.67 (d, $J = 7.5$ Hz, 1H); 6.15-6.19 (m, 1H); 6.43 (s, 1H); 7.35-7.39 (m, 5H); 7.47-7.51 (m, 4H); 7.59 (t, $J = 7.5$ Hz, 1H); 7.64 (t, $J = 7.5$ Hz, 1H); 8.08 (d, $J = 7.5$ Hz, 2H); 8.25 (d, $J = 7.5$ Hz, 2H) [ppm]

The product of condensation was treated with 0.1 N HCl in methanol, and the final product was chromatographically purified on silica gel with the system of hexane: ethyl

acetate 1.5:1. It gave 0.594 g (i.e. yield 76%) of a product spectroscopically and chromatographically identical to Paclitaxel.

15. Example

Solution of 2-chlor-4,6-diphenoxy-1,3,5-triazine (0.3 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to obtain N-(4,6-diphenoxy-1,3,5-triazine-2-yl)-N-methylmorpholine chloride. Then, phenyl isoserine derivative with the formula **4c**, (0.267 g, 1 mmol) was added and mixed for 12 hours. After N-methylmorpholine hydrochloride was filtered off, and solvent was evaporated, it gave respective triazine ester of the formula **6c**, where $R_5=R_6=OC_6H_5$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.65$

1H -NMR (250 MHz, $CDCl_3$): $\delta=5.31$ (d, $J=7.5$ Hz, 1H); 5.57 (d, $J=7.5$ Hz, 1H); 7.12-7.50 (m, 18H); 8.13 (d, $J=8.0$ Hz, 2H) [ppm]

IR (KBr): 1790 [cm^{-1}]

The triazine ester, in the presence of 4-pyrrolidinopyridine, was coupled with protected Baccatin III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. The product was chromatographically and spectrally identical to that described in the 14. Example.

16. Example

Solution of 2,4-dichlor-6-methoxy-1,3,5-triazine (0.09 g, 0.5 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to obtain respective quaternary triazinammonium salt. Then, phenyl isoserine derivative with the formula **4c**, (0.267 g, 1 mmol) was added and mixed for 12 hours, first at temperature of 0-5°C, next at room temperature. After N-methylmorpholine hydrochloride was filtered off, and solvent was evaporated, it gave respective triazine ester of the formula **6c**, where $R_5=OC_6H_5$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.55$

1H -NMR ($CDCl_3$): $\delta=3.76$ (s, 3H); 5.31 (d, $J=7.5$ Hz, 2H); 5.56 (d, $J=7.5$ Hz, 2H); 7.35-7.47 (m, 12H); 7.75-7.77 (m, 4H); 8.04 (d, $J=8.0$ Hz; 4H)[ppm]

IR (KBr): 1785 [cm^{-1}]

The triazine ester was coupled with protected Baccatin III of generalized formula **3**, where $R_2=Si(C_2H_5)_3$, in the presence of magnesium bromide and diazobicycloundekane. It gave product chromatographically and spectrally identical to that of the 14 Example.

17. Example

Solution of 2-chlor-4,6-methoxy-1,3,5-triazine (0.175 g, 1 mmole) in 5 ml THF was mixed with N-methylmorpholine (0.11 ml, 1 mmole) for 30 minutes at temperature of 0-5°C to

obtain respective quaternary triazinammonium salt. Then, phenyl isoserine derivative with the formula **4a**, where $R_2 = H$ (0.267 g, 1 mmol) was added and mixed for 12 hours, first at temperature of $0-5^{\circ}C$, next at room temperature. After N-methylmorpholine hydrochloride was filtered off, and solvent was evaporated, it gave respective triazine ester of the formula **6a**, where $R_2=H$, $R_5 = OC_6H_5$, with the quantitative yield.

TLC: eluent $CHCl_3$, $R_f=0.4$

1H -NMR ($CDCl_3$): $\delta = 3.86$ (s, 6H); 5.41 (d, $J=7.8$ Hz, 1H); 5.72 (d, $J=7.8$ Hz, 1H); 7.00-7.38 (m, 8H); 7.44 (d, $J=8.0$ Hz; 2H)[ppm]

IR (KBr): 1795 [cm^{-1}]

For 5 days the triazine ester, in the presence of 4-(N,N-dimethylamino)pyridine and magnesium bromide was coupled with protected Baccatin III of the generalized formula **3**, where $R_2=Si(C_2H_5)_3$. It gave 0.800 g (yield 81%) of the product characterized by $R_f=0.65$ (eluent acetone: benzene 1:4), which without purification was treated with concentrated hydrochloric acid in tetrahydrofuran for 10 min. After purification on silica gel in a chromatographic column in the mixture of hexane and ethyl acetate 1:1 as the movable phase, it was obtained 0.482 g (yield 70%) of the product spectroscopically and chromatographically identical to Paclitaxel described in the 1. Example.

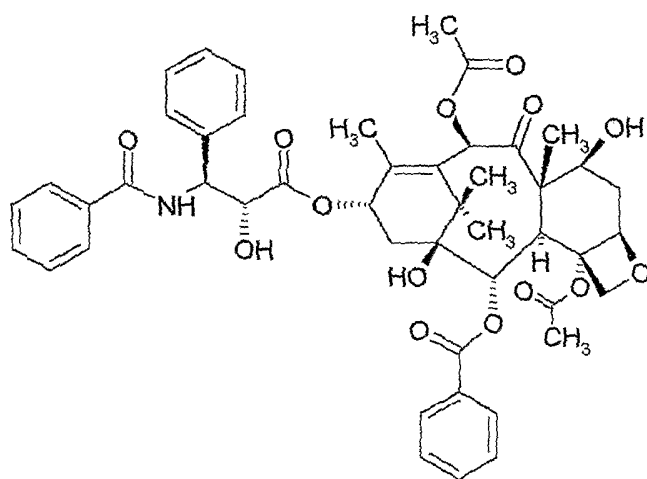
Patent claims

1. The method for production of semi-finished products useful in synthesis of Paclitaxel, of the generalized formula 2, where R_1 denotes the group with the formula 7, or with the formula 8, or with the formula 9, or with the formula 10, R_2 denotes hydrogen, alkylsilol group or substituted alkylsilol group, arylsilol group or substituted arylsilol group, alkylarylsilol group or substituted alkylarylsilol group, alkoxycarbonyl group or substituted alkoxycarbonyl group, alkoxymethyl group or substituted alkoxymethyl group, R_3 and R_4 denote hydrogen, alkyl group, substituted alkyl group, aryl group, substituted aryl group, whereas X denotes $C=O$, $C=S$, $S=O$, SO_2 , $(C=O)_2$, $P(aryl)_3$, $P-N(alkyl)_2$, $(P=O)-N(alkyl)_2$, $(P=S)-N(alkyl)_2$ groups, by reaction of Baccatin III derivative and phenyl isoserine derivative, characterized in that phenyl isoserine derivatives with generalized formulas 4a-d, in which R_2 , R_3 , R_4 and X have above specified meanings, or mixtures of their epimerides with different configurations on the carbon 2' or their salts are treated with triazine condensing agent having the generalized formula 5, in which R_5 and R_6 denote chlorine, alkyloxylic group, substituted alkyloxylic group, aryloxylic group, substituted aryloxylic group, whereas R_7 denotes fluorine, chlorine or quaternary ammonium group, possibly in the presence of anhydrous organic solvent, next so obtained triazine esters of phenyl isoserine with generalized formulas 6a-d, in which R_2 , R_3 , R_4 and X have above specified meanings, is reacted with Baccatin III, with the generalized formula 3, where R_2 denotes hydrogen or a group which protects the hydroxyl group in the position 7, in an anhydrous organic solvent, in the presence of a catalyst if required.
2. The method according to claim 1, characterized in that the groups protecting the hydroxyl function in the 7. Position of Baccatin there are used alkylsilol group or substituted alkylsilol group, arylsilol group or substituted arylsilol group, alkylarylsilol group or substituted alkylarylsilol group, alkoxycarbonyl group or substituted alkoxycarbonyl group, alkoxymethyl group or substituted alkoxymethyl group.
3. The method according to claim 2, characterized in that as the group protecting the hydroxyl function in the 7. Position of Baccatin there is used triethylsilol group.

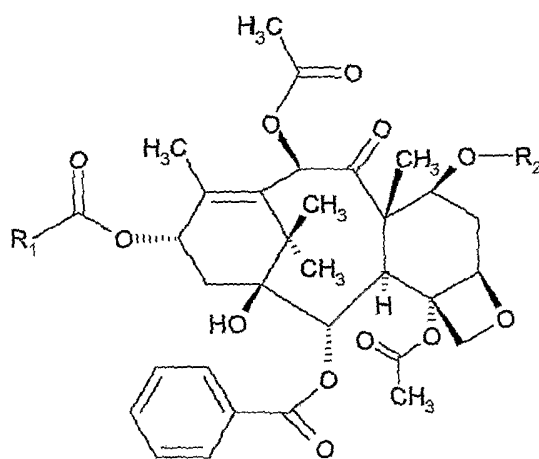
4. The method according to claim 1, characterized in that as the salts of phenyl isoserine derivatives metal salts are used, particularly alkali metal salts or tertiary amine salts, preferable of N-methylmorpholine.
5. The method according to claim 1, characterized in that as triazin based condensing agent 2-chloro-4,6-dimethoxy-1,3,5-triazine is used.
6. The method according to claim 1, characterized in that as triazin based condensing agent quaternary triazinilammonium salt is used, obtained by treatment of tertiary amine with 2-chlor-4,6-dimethoxy-1,3,5-triazine.
7. The method according to claim 1, characterized in that as tertiary amine N-methylmorpholine, tetramethylguanidyne, 1,4-dimethylpiperazyne, N-methylpyrrolidyne, N,N'-tetramethyloethyldiamine, N-methylpiperidyne, pyridine, pyridine derivatives substituted in the carbon atom in the pyridine ring or diazabicycloundekane are used.
8. The method according to claim 1, characterized in that triazin esters with the generalized formulas 6a-d are removed from the reaction mixture before treatment with Baccatin derivatives.
9. The method according to claim 1, characterized in that reaction with Baccatin is accomplished in the presence of a Lewis type acid.
10. The method according to claim 9, characterized in that the Lewis type acid is anhydrous magnesium bromide.
11. The method according to claim 1, characterized in that reaction with Baccatin is accomplished in the presence of a base.
12. The method according to claim 11, characterized in that as the base tertiary amine is used.
13. The method according to claim 11, characterized in that as the tertiary amine 4-(N,N-dimethylamino)pyridine or 4-(pyrrolidin-1)pyridine or 1,8-diazabicyclo[5.4.0.]undec-7-en are used.
14. The method according to claim 1, characterized in that reaction with Baccatin is accomplished with use of anhydrous magnesium bromide in the presence of 4-(N,N-dimethylamino)pyridine or 4-(pyrrolidino-1)pyridine or 1,8-diazabicyclo[5.4.0.]undec-7-ene.
15. The method according to claim 1, characterized in that as solvent a-proton solvent is used.
16. The method according to claim 15, characterized in that as solvent aromatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, acidamides, acidonitriles are used.

17. The method according to claim 16, characterized in that as solvent toluene, dichloromethane, dichloroethane, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide and phosphoric acid N,N',N'-hexamethylamide, acetonitrile are used.

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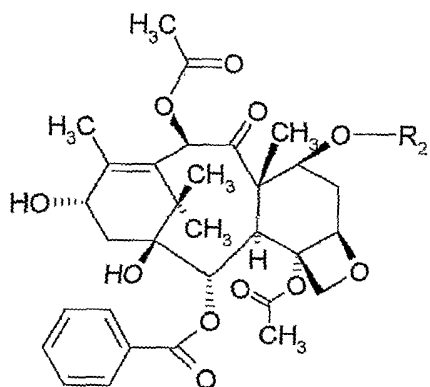


Formula 1.

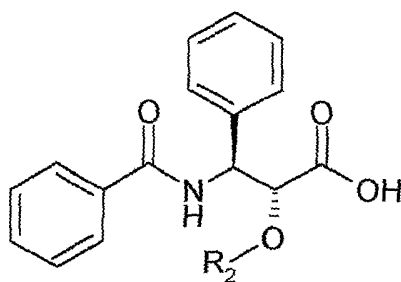


Formula 2.

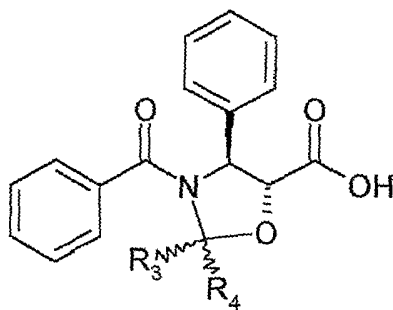
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Formula 3.

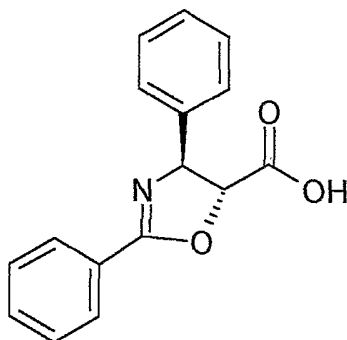


Formula 4a

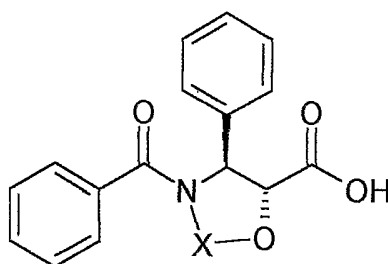


Formula 4b

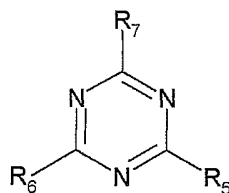
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Formula 4c

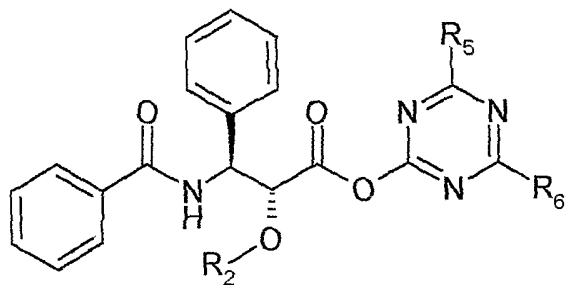


Formula 4d

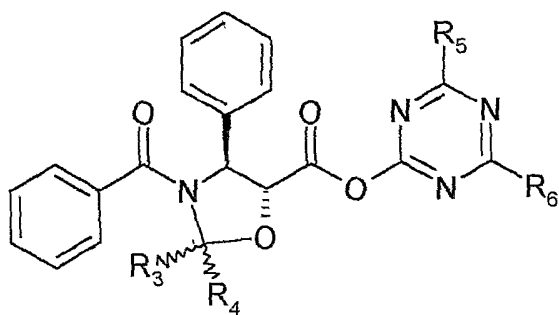


Formula 5.

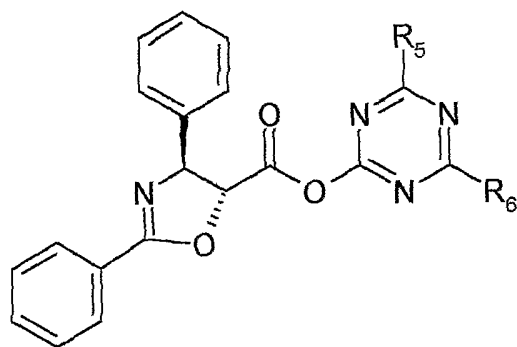
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Formula 6a

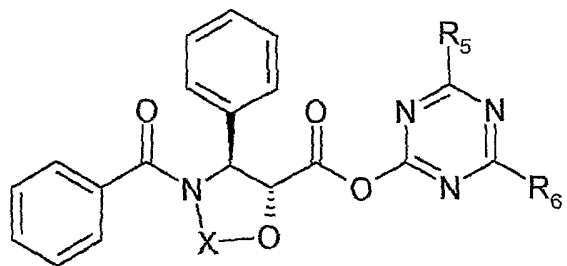


Formula 6b

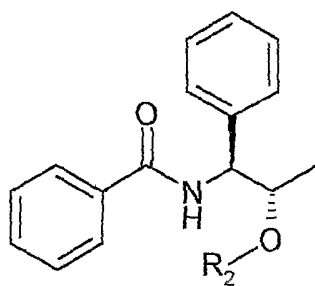


Formula 6c

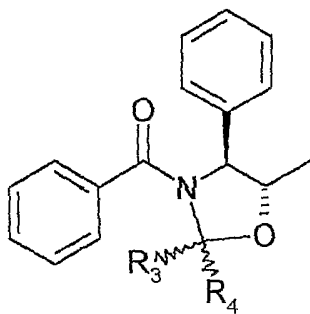
5/6



Formula 6d

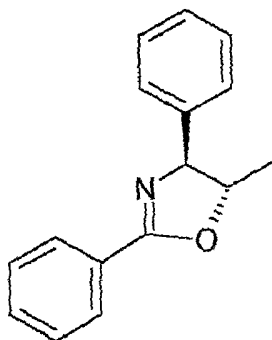


Formula 7.

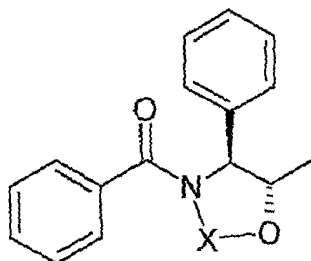


Formula 8.

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Formula 9.



Formula 10.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/PL 03/00139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D305/04

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)
IPC 7 C07D

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93/06079 A (FLORIDA STATE UNIVERSITY) 1 April 1993 (1993-04-01) cited in the application claims; examples	1-17
A	US 6 150 537 A (LIOTTA ET. AL.) 21 November 2000 (2000-11-21) cited in the application column 15, line 1 -column 18, line 45; claims 1,6	1-17
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *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 when the document is taken alone
- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

13 April 2004

Date of mailing of the international search report

20/04/2004

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL 03/00139

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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