



(43) International Publication Date
12 January 2017 (12.01.2017)

- (51) International Patent Classification:
C12P 17/00 (2006.01) C12P 19/28 (2006.01)
- (21) International Application Number:
PCT/EP2016/065958
- (22) International Filing Date:
6 July 2016 (06.07.2016)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
15175659.0 7 July 2015 (07.07.2015) EP
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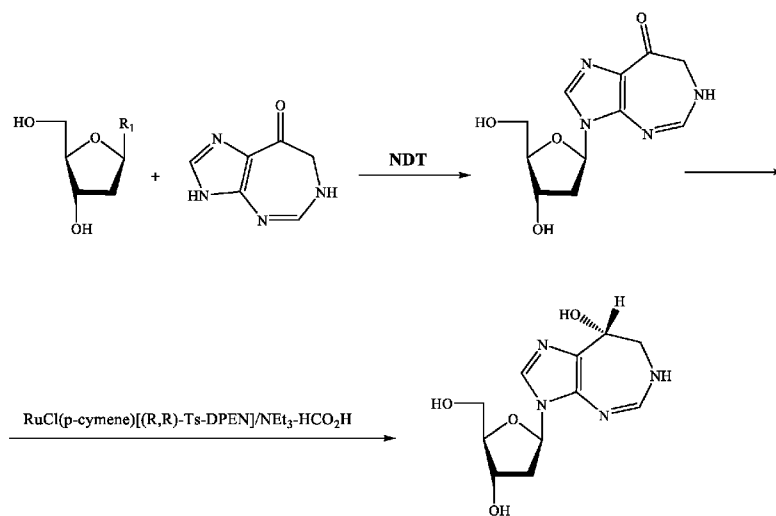
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: METHOD FOR THE SYNTHESIS OF PENTOSTATIN

FIGURE 3



(57) Abstract: The present invention relates to a method for the stereo-selective production of pentostatin comprising an enzymatic transglycosylation reaction between 6,7-dihydroimidazo-[4,5-d]-[1,3]diazepin-8(3H)-one and a 2'-deoxyribonucleoside, followed by a ruthenium-catalyzed asymmetric transfer hydrogenation.

METHOD FOR THE SYNTHESIS OF PENTOSTATIN

FIELD OF THE INVENTION

The present invention relates to a method for the stereo-selective production of pentostatin comprising an enzymatic transglycosylation reaction between 6,7-dihydroimidazo-[4,5-d]-[1,3]diazepin-8(3*H*)-one and a 2'-deoxyribonucleoside, followed by an ruthenium-catalyzed asymmetric transfer hydrogenation. The method results in the production of pentostatin in high yield and with a > 99% excess of the desired β -anomer.

BACKGROUND OF THE INVENTION

Pentostatin is a cytostatic purine analogue acting as one of the most potent inhibitors of adenosine deaminase that is used for the treatment of various types of lymphoproliferative disorders. The systematic name of pentostatin is (R)-3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,6,7,8-tetrahydro-imidazo[4,5-d]-[1,3]diazepin-8-ol) and its chemical structure is illustrated in **FIG.1**.

Currently, the primary method for the large-scale production of pentostatin relates to the fermentation of *Streptomyces anlibilicus* NRRL 3238 cultures. However this method has several serious drawbacks including a very low yield of the final product (only about 13 g from 1000 l of fermentative broth) as well as a complicated and expensive chromatography purification process (Woo, P.W.K. et al. (1974) *J. Heterocycl. Chem.* **11**, 641-645).

The total chemical synthesis of pentostatin poses a challenge since the molecule contains (i) a unique and unstable heterocyclic base, (ii) a 2-deoxy sugar that defies attempts at stereo-controlled glycosylation to favor the β -anomer, and (iii) a central chiral hydroxyl group. The merit of any chemical transformation is measured by its resolutions to these three key difficulties.

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The first synthesis scheme of pentostatin was established in 1979 (Baker, D.C., and Putt, S.R. (1979) *J. Am. Chem. Soc.* **101**, 6127-6128). The synthesis route is schematically depicted in **FIG. 2** and included a total of eleven steps. It involves the production of an imidazo[4,5-*d*]-[1,3]diazepine heterocyclic compound followed by non-selective glycosidation (with the portion of the desired β -anomer representing only 14%) and reduction. The overall yield is only 1.6% (as compared to the starting materials),

Subsequently, several modifications and improvements of this method were established (see, e.g., Chan, E. et al. (1982) *J. Org. Chem.* **47**, 3457-3464; Chen, B.C. et al. (2002) *Tetrahedron Lett.* **43**, 1595-1596; Ho, J.Z. et al. (2003) *J. Org. Chem.* **68**, 109-114), all of which are still hampered by the rather low yield due to the lack of stereo-specificity during individual synthesis steps.

WO 2014/177585 A2 discloses a synthesis scheme employing as starting material an imidazo[4,5-*d*]-[1,3]diazepine heterocyclic compound including a hydroxyl functionality. However, this process requires the long-time heating of the reaction mixture at 50°C, which may lead to the formation of undesirable by-products.

WO 2005/027838 A2 discloses a synthesis scheme for the production of pentostatin comprising a ring expansion of an O-C-N functionality in a hypoxanthine or 2-deoxyinosine derivative, resulting in an improved yield. However, due to its overall chemical complexity this synthesis route is also not suitable for the large-scale production of pentostatin.

Hence, there is still an ongoing need for improved methods for the synthesis of pentostatin that overcome the limitations of the established synthesis routes. In particular, there is a need for a less laborious and cost-efficient method for the large-scale production of pentostatin, thus improving stereo-specificity of the individual reaction steps in favor of the desired β -anomer of (8-R)-pentostatin.

Accordingly, it is an object of the present invention to provide an improved method for the synthesis of pentostatin.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a method for the stereo-selective synthesis of the pentostatin, comprising: (i) reacting 6,7-dihydroimidazo-[4,5-*d*]-[1,3]diazepin-8(3*H*)-one and a 2-deoxy-ribonucleoside; and (ii) reducing the 8-keto pentostatin derivative obtained in step (i) by ruthenium-catalyzed asymmetric transfer hydrogenation; wherein the reaction in step (i) is enzymatically catalyzed by nucleoside deoxyribosyltransferase.

In a preferred embodiment, the 2-deoxy-ribonucleoside used is 2-deoxy-uridine.

In a particular embodiment, the 2-deoxy-ribonucleoside is used in an amount of 1.5 to 10 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one. Preferably, the 2-deoxy-ribonucleoside is used in an amount of 4 to 7 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one compound.

In another particular embodiment, the reaction in step (i) is performed at a temperature between 10°C and 50°C. Preferably, the reaction in step (i) is performed at a temperature between 25°C and 35°C.

In another particular embodiment, the reaction in step (i) is performed at a pH value between 6.0 and 9.0. Preferably, the reaction in step (i) is performed at a pH value between 7.5 and 8.0.

In a preferred embodiment, the reaction in step (ii) is catalyzed by RuCl(*p*-cymene)[(R,R)-Ts-DPEN]. Particularly preferably, the reaction in step (ii) is performed in a mixture of triethylamine and formic acid.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 illustrates the chemical structure of (R)-3-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol) (i.e., pentostatin).

FIGURE 2 illustrates a representative synthesis scheme for the production of pentostatin being established in the art.

FIGURE 3 illustrates a representative synthesis scheme for the stereo-selective production of pentostatin according to the present invention.

FIGURE 4 illustrates a representative HPLC chromatogram of the reaction mixture after reduction of 8-keto pentostatin using NaBH₄ in methanol in accordance to the established synthesis scheme described in Chan, E. et al. (1982) *J. Org. Chem.* **47**, 3457-3464. The chromatogram reveals the concomitant presence of both pentostatin (i.e. the 8-R isomer) and the contaminating 8-S isomer in a ratio of about 55% to 45%.

FIGURE 5 illustrates a representative HPLC chromatogram of the reaction mixture after reduction of unprotected 8-keto pentostatin using a ruthenium-catalyzed asymmetric transfer hydrogenation according to the present invention. The chromatogram reveals the (almost) exclusive presence of the desired 8-R isomer (i.e., pentostatin). The 8-S isomer is only present as remnant in an amount of about 0.2%.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the unexpected finding that combining an enzymatic transglycosylation reaction of 6,7-dihydroimidazo-[4,5-*d*]-[1,3]diazepin-8(3*H*)-one with a 2-deoxy-ribonucleoside and a subsequent ruthenium-catalyzed asymmetric transfer hydrogenation, performed on the unprotected 8-keto pentostatin derivative obtained, results in a significant increase in yield of pentostatin (about 4-fold as compared to established methods) by shifting stereo-selectivity of the overall reaction towards a huge excess of, and preferably completely to the desired β -anomer of (8-R)-pentostatin. Without intending to be bound by any theory it is tempting to assume that the presence of the keto-group is critical for preventing the formation of undesired stereoisomers at carbon C-8 so that in the subsequent step the 8-keto pentostatin derivative obtained can be employed in unprotected form, which makes the overall synthesis scheme significantly less laborious.

The present invention will be described in the following with respect to particular embodiments and with reference to certain drawings but the invention is to be understood as not limited thereto but only by the appended claims. The drawings described are only schematic and representative and are to be considered non-limiting.

Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. For the purposes of the present invention, the term "consisting of" is considered to be a preferred embodiment of the term "comprising". If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also to be understood to disclose a group, which preferably consists only of these embodiments.

Where an indefinite or definite article is used when referring to a singular noun e.g. "a", "an" or "the", this includes a plural of that noun unless specifically stated otherwise.

In case, numerical values are indicated in the context of the present invention the skilled person will understand that the technical effect of the feature in question is ensured within an interval of accuracy, which typically encompasses a deviation of the numerical value given of $\pm 10\%$, and preferably of $\pm 5\%$.

Furthermore, the terms first, second, third, (a), (b), (c), and the like in the description and in the claims, are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

Further definitions of term will be given in the following in the context of which the terms are used. The following terms or definitions are provided solely to aid in the understanding of the invention. These definitions should not be construed to have a scope less than understood by a person of ordinary skill in the art.

In one aspect, the present invention relates to a method for the stereo-selective synthesis of the pentostatin, comprising:

- (i) reacting 6,7-dihydroimidazo-[4,5-*d*]-[1,3]diazepin-8(3*H*)-one and a 2-deoxy-ribonucleoside; and
- (ii) reducing the 8-keto pentostatin derivative obtained in step (i) by ruthenium-catalyzed asymmetric transfer hydrogenation;

wherein the reaction in step (i) is enzymatically catalyzed by nucleoside deoxyribosyltransferase.

The transglycosylation reaction in step (i) is catalyzed by nucleoside deoxyribosyltransferase (i.e., nucleoside:purine(pyrimidine) deoxy-D-ribosyltransferase having the EC number 2.4.2.6). This enzyme catalyzes the general reaction: 2-deoxy-D-ribosyl-base¹ + base² = 2-deoxy-D-ribosyl-base² + base¹. Typically, the enzyme employed is a recombinant enzyme, being commercially available from various suppliers.

The 6,7-dihydroimidazo-[4,5-*d*]-[1,3]diazepin-8(3*H*)-one may be reacted with any 2-deoxy-ribonucleosides, such as naturally occurring 2-deoxy-ribonucleosides as well as artificially produced analogs thereof. Examples of suitable 2-deoxy-ribonucleosides include 2-deoxy-adenosine, 2-deoxy-cytosine, 2-deoxy-guanine, 2-deoxy-uridine, 2-deoxy-thymidine, 2-deoxy-inosine, and 5-aza-derivatives thereof.

In a preferred embodiment, the 2-deoxy-ribonucleoside used is 2-deoxy-uridine.

Since the transglycosylation reaction in step (i) is reversible, the amount of 2-deoxy-ribonucleoside used is typically higher than the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one, that is, the 2-deoxy-ribonucleoside is used in a molar excess.

In a particular embodiment, the 2-deoxy-ribonucleoside is used in an amount of 1.5 to 10 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one. Preferably, the 2-deoxy-ribonucleoside is used in an amount of 4 to 7 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one. For example, the 2-deoxy-ribonucleoside is used in an amount of 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, 5.2, 5.4, 5.6, 5.8, 6.0, 6.2,

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6.4, 6.6, 6.8, or 7.0 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one, with a molar excess of 5.6, 5.8 or 6.0 being particularly preferred.

Typically the reaction in step (i) is performed at a temperature between 10°C and 50°C. Preferably, it is performed at a temperature between 25°C and 35°C. For example, the reaction in step (i) may be performed at a temperature of 25°C, 28°C, 30°C, 32°C or 35°C.

Furthermore, the reaction in step (i) typically is performed at a pH value between 6.0 and 9.0. Preferably, it is performed at a pH value between 7.5 and 8.0. For example, the reaction in step (i) may be performed at a pH of 7.5, 7.6, 7.7, 7.8, 7.9 or 8.0.

Due to the stereo-specificity of enzymatic transglycosylation, the only product is the desired β -anomer, that is, the 8-keto pentostatin derivative, which further results in a significant simplification of the synthesis scheme as there is no need for additional purification steps in order to remove the α -anomer. The yield of the 8-keto pentostatin derivative obtained is thus up to two-fold higher as compared to established glycosylation methods.

US 20090012288 A1 describes the preparation of a ruthenium catalyst by the reaction of di- μ -chlorobis[(*p*-cymene)chlororuthenium] and *N*-(arylsulfonyl)-1,2-diarylethylene diamine and the use of this catalyst for the stereo-selective reduction of a protected 8-keto pentostatin derivative. However, it could not be expected offhand that a ruthenium catalyst also works in an asymmetric transfer hydrogenation performed on an unprotected derivative. Rather, it was reasonable to assume the formation of a significant amount of side products.

In a preferred embodiment, the reaction in step (ii) is catalyzed by RuCl(*p*-cymene)[(R,R)-Ts-DPEN] (i.e., [*N*-[(1*R*,2*R*)-2-(amino- κ *N*)-1,2-diphenylethyl]-4-methylbenzenesulfonamidato- κ *N*]chloro[(1,2,3,4,5,6- η)-1-methyl-4-(1-methylethyl)benzene]-ruthenium).

Particularly preferably, the reaction in step (ii) is performed in a mixture of triethylamine and formic acid, that is, under comparably mild reaction conditions. Typically, the mixture employed comprises 3 volumes of triethylamine and 1 volume of formic acid.

The reaction condition employed in step (ii) result in a shift towards a > 99% excess of the desired 8-R isomer.

As a result, the method of the present invention results in an up to 4-fold increase in yield of the final reaction product pentostatin as compared to methods established in the art.

The invention is further described by the figures and the following examples, which are solely for the purpose of illustrating specific embodiments of this invention, and are not to be construed as limiting the claimed subject matter in any way.

EXAMPLES

Example 1: Synthesis of 3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)-tetrahydro-furan-2-yl)-6,7-dihydroimidazo[4,5-d]-[1,3]diazepin-8(3H)-one

1.5 g of potassium chloride was dissolved in 0.5 l of 20 mM phosphate buffer, pH 8.0. Then, 10 g of 2'-deoxyuridine and 20 ml of nucleoside deoxyribosyltransferase solution (10 mg/ml) were added under stirring. The resulting solution was heated to 25-30°C and 2.0 g of 6,7-dihydroimidazo-[4,5-d][1,3]diazepin-8(3H)-one hydrochloride monodimethyl-sulfoxide were added. The reaction mixture was stirred at 25-30°C for 3 hours. The resulting product was purified using low-pressure reverse phase column chromatography to obtain 1.58 g (78%) of pure substance (more than 99% purity as determined by HPLC).

Example 2: Synthesis of (R)-3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)-tetrahydro-furan-2-yl)-3,6,7,8-tetrahydroimidazo[4,5-d]-[1,3]diazepin-8-ol (i.e. pentostatin).

Under N₂ atmosphere, 1.0 g of 3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-6,7-dihydroimidazo[4,5-d]-[1,3]diazepin-8(3H)-one was added to a flask with 20 mg of RuCl(*p*-cymene)[(R,R)-Ts-DPEN]. A degassed mixture of 10 ml of triethylamine and 3.3 ml of formic acid was added. The reaction mixture was stirred one day at 40°C under N₂ purging until > 99% conversion was achieved (as determined by HPLC). Afterwards, the reaction mixture was poured into 200 ml of 100 mM phosphate buffer, pH 7.5. The product was

purified using low-pressure reverse phase column chromatography to obtain 0.84 g (83%) of pure pentostatin with an 8R/8S isomer ratio of about 1000:1 (as determined by HPLC).

The ratio of 8-R/8-S isomers of pentostatin was determined by HPLC. **FIGURE 5** illustrates a representative HPLC chromatogram of the reaction mixture after reduction of unprotected 8-keto pentostatin using a ruthenium-catalyzed asymmetric transfer hydrogenation according to the present invention. The chromatogram reveals the (almost) exclusive presence of the desired 8-R isomer (i.e., pentostatin) in an amount of about 99.8% (retention time: 9.7 min). The unwanted 8-S isomer is only present as remnant in an amount of about 0.2% (retention time: 8.0 min)

As a comparative example, pentostatin was produced in accordance to the established synthesis scheme described in Chan, E. et al. (1982) *J. Org. Chem.* **47**, 3457-3464. The reaction scheme includes the reduction of 8-keto pentostatin using NaBH₄ in methanol. **FIGURE 4** illustrates a representative HPLC chromatogram of the reaction mixture after the reduction step. The chromatogram reveals the concomitant presence of pentostatin (i.e. the 8-R isomer) in an amount of 54.3% (retention time: 9.4 min) and the contaminating 8-S isomer in an amount of 45.7% (retention time: 8.2 min), respectively, thus demonstrating the superior properties of the synthesis scheme of the present invention.

The present invention illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by embodiments and optional features, modifications and variations of the inventions embodied therein may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

The invention has been described broadly and generically herein. Each of the narrower species and sub-generic groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

CLAIMS

1. Method for the stereo-selective synthesis of the pentostatin, comprising:
 - (i) reacting 6,7-dihydroimidazo-[4,5-*d*]-[1,3]diazepin-8(3*H*)-one and a 2-deoxy-ribonucleoside; and
 - (ii) reducing the 8-keto pentostatin derivative obtained in step (i) by ruthenium-catalyzed asymmetric transfer hydrogenation;wherein the reaction in step (i) is enzymatically catalyzed by nucleoside deoxyribosyltransferase.
2. The method of claim 1, wherein the 2-deoxy-ribonucleoside is 2-deoxy-uridine.
3. The method of claim 1 or 2, wherein the 2-deoxy-ribonucleoside is used in an amount of 1.5 to 10 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one.
4. The method of claim 3, wherein the 2-deoxy-ribonucleoside is used in an amount of 4 to 7 molar equivalents of the amount of 6,7-dihydroimidazo[4,5-*d*]-[1,3]diazepin-8(3*H*)-one.
5. The method of any one of claims 1 to 4, wherein the reaction in step (i) is performed at a temperature between 10°C and 50°C.
6. The method of claim 5, wherein the reaction in step (i) is performed at a temperature between 25°C and 35°C.
7. The method of any one of claims 1 to 6, wherein the reaction in step (i) is performed at a pH value between 6.0 and 9.0.
8. The method of claim 7, wherein the reaction in step (i) is performed at a pH value between 7.5 and 8.0.

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9. The method of any one of claims 1 to 8, wherein the reaction in step (ii) is catalyzed by $\text{RuCl}(\rho\text{-cymene})[(R,R)\text{-Ts-DPEN}]$.
10. The method of claim 9, wherein the reaction in step (ii) is performed in a mixture of triethylamine and formic acid.

FIGURE 1

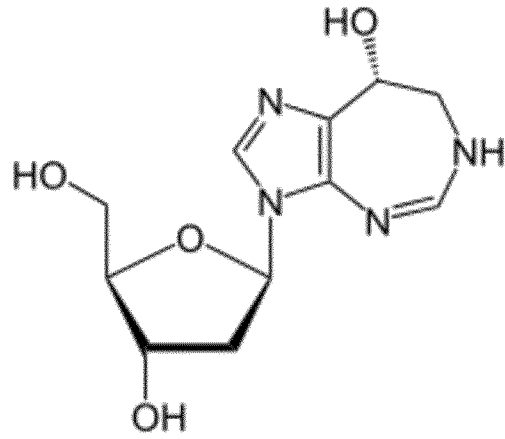


FIGURE 2

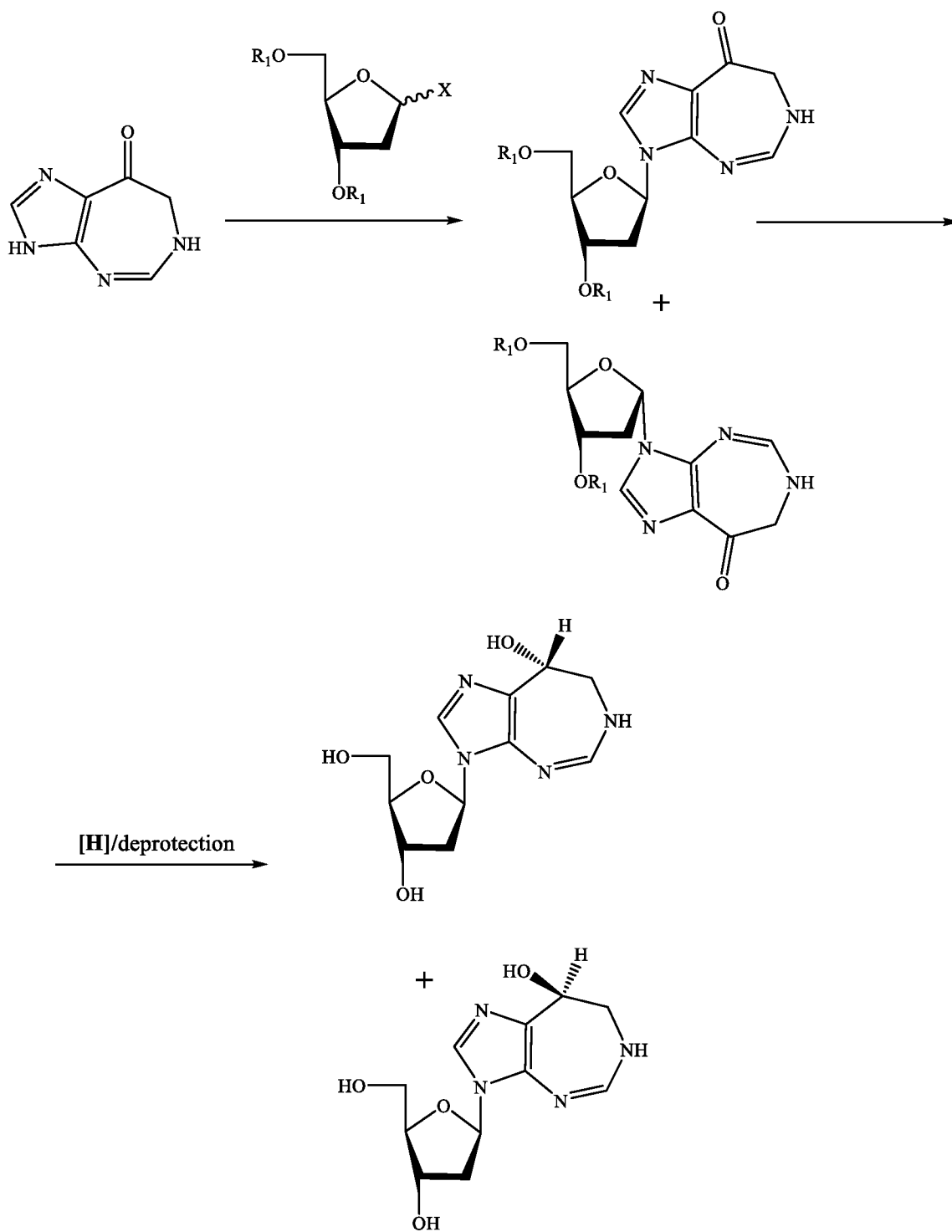


FIGURE 3

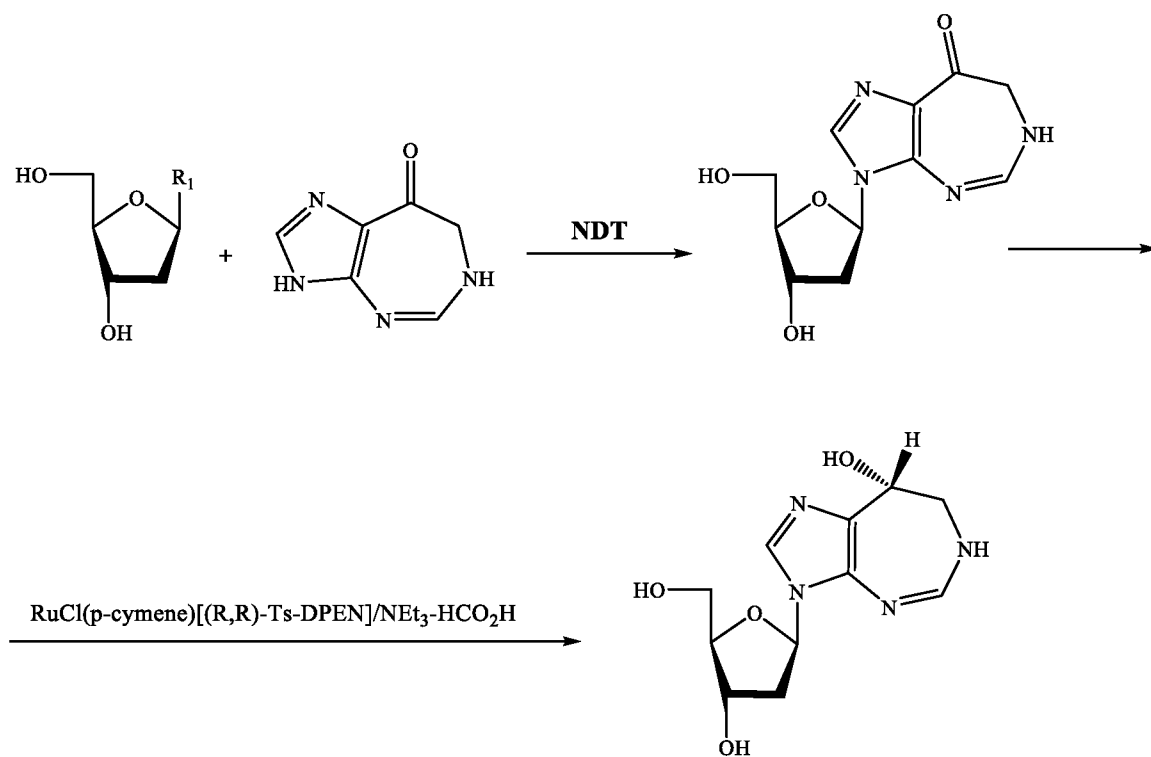


FIGURE 4

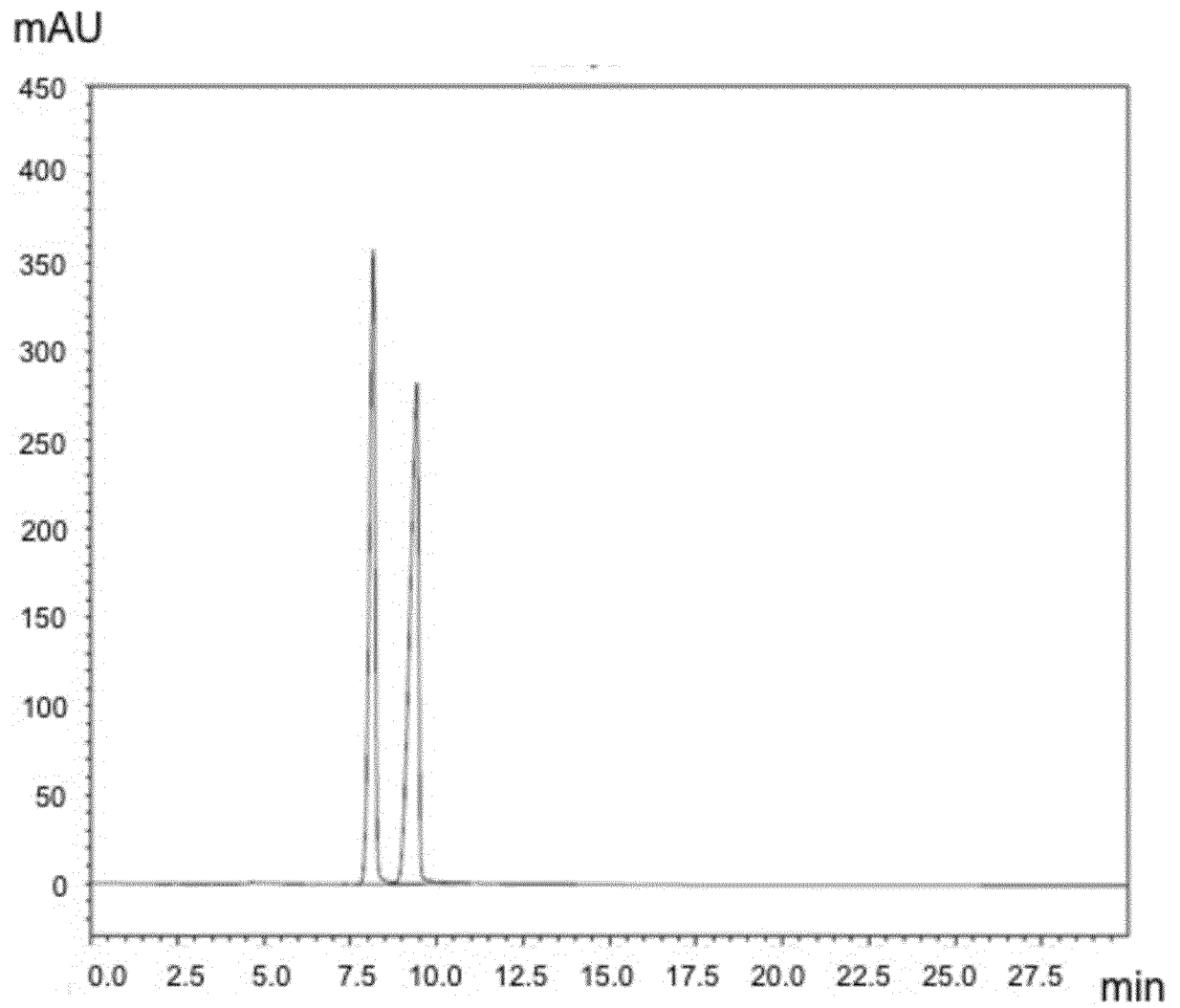
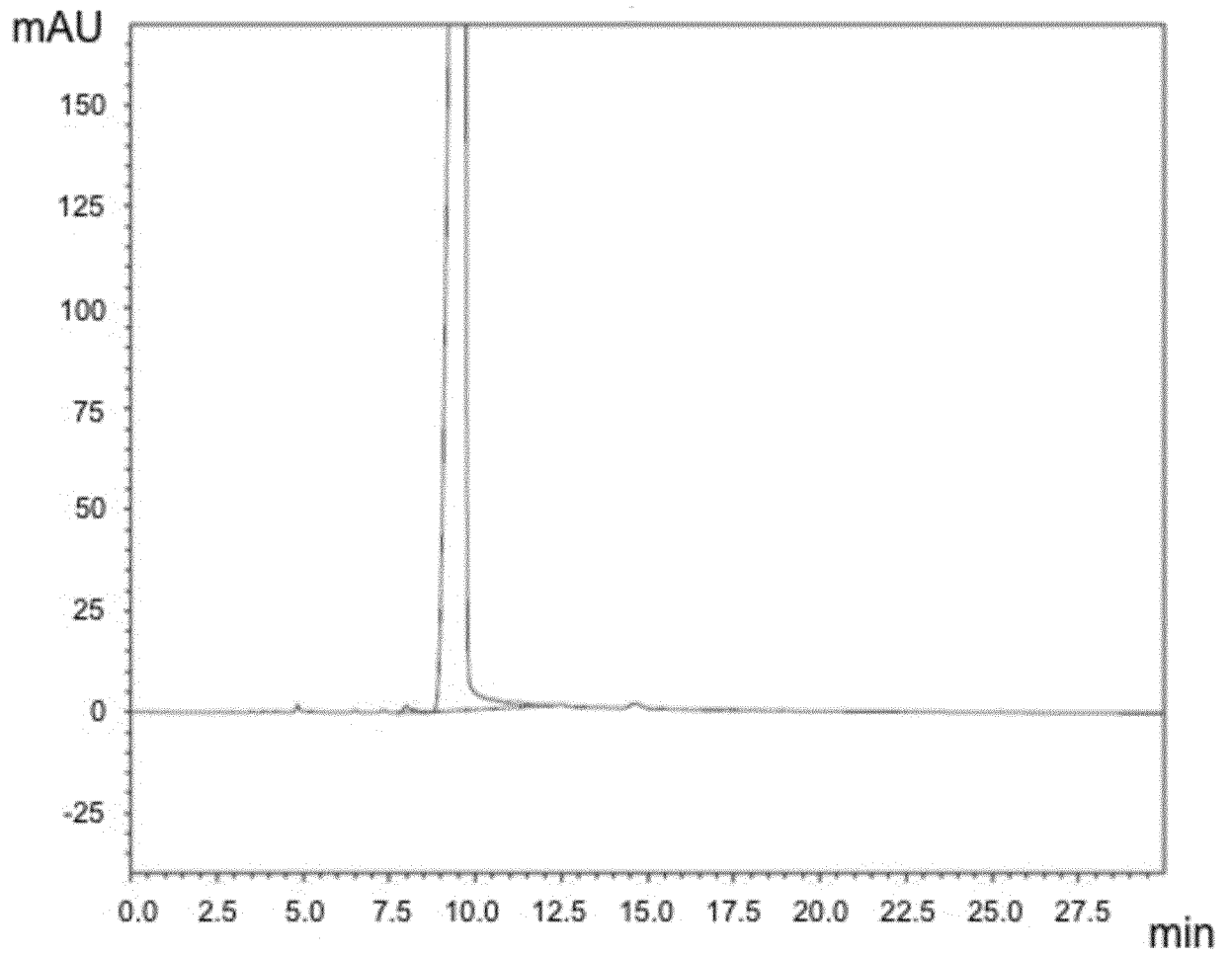


FIGURE 5



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065958

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12P17/00 C12P19/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C12P
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI 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 2014/177585 A2 (PLASMIA BIOTECH S L [ES]) 6 November 2014 (2014-11-06) page 17, line 19 - page 19, line 7; claims 1-3 page 26, lines 13-24 -----	1-10
A	US 2009/012288 A1 (ZHANG HAI-REN [US] ET AL) 8 January 2009 (2009-01-08) cited in the application paragraphs [0006], [0007], [0022], [0023]; claim 6 -----	1-10
A	WO 2005/027838 A2 (SUPERGEN INC [US]; PHIASIVONGSA PASIT [US]; REDKAR SANJEEV [US]) 31 March 2005 (2005-03-31) cited in the application claims ----- -/--	1-10

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 16 August 2016	Date of mailing of the international search report 25/08/2016
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Boeker, Ruth

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065958

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>E. CHAN ET AL: "Total Synthesis of (8R)-3-(2-Deoxy-beta-D-erythro-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-d][1,3]diazepin-8-ol (Pentostatin), the Potent Inhibitor of Adenosine Deaminase", J. ORG. CHEM, vol. 47, 1982, pages 3457-3464, XP055295525, cited in the application the whole document</p> <p style="text-align: center;">-----</p>	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/065958

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