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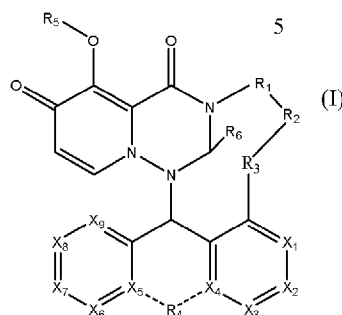
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(54) Title: MACROCYCLIC FLU ENDONUCLEASE INHIBITORS



(57) Abstract: The present invention relates to macrocyclic pyridotriazine derivatives of formula (I) and the pharmaceutically acceptable salts, solvates or or polymorph thereof, and the use of such compounds as a medicament, in particular in the prevention and/or treatment of viral infections caused by viruses belonging to the *Orthomyxoviridae* family. The present invention furthermore relates to pharmaceutical compositions or combination preparations of the compounds, and to the compositions or preparations for use as a medicament, more preferably for the prevention or treatment of viral infections caused by viruses belonging to the *Orthomyxoviridae* family.



MACROCYCLIC FLU ENDONUCLEASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to macrocyclic compounds, in particular macrocyclic pyridotriazine derivatives and the prodrugs thereof, to methods to prevent or treat influenza viral infections by using said compounds and to said compounds for use as a medicine, more preferably for use as a medicine to treat or prevent influenza viral infections. The present invention also relates to pharmaceutical compositions or combination preparations of the compounds, to the compositions or preparations for use as a medicine, more preferably for the prevention or treatment of influenza viral infections.

BACKGROUND OF THE INVENTION

Influenza is a serious public health problem with high incidence in the human population resulting in regular large-scale morbidity and mortality. According to the WHO the average global burden of annual epidemics may be on the order of 1 billion cases, 3-5 million cases of severe illness and 300,000–500,000 deaths annually. In the US, annual influenza epidemics lead to approximately 30 million outpatient visits, resulting in medical costs of \$10 billion annually. Lost earnings due to illness and loss of life represent a cost of over \$15 billion annually and the total US economic burden of annual influenza epidemics amounts to over \$85 billion.

Pathogens that cause influenza are negative sense, single-stranded RNA viruses, which belong to the family of *Orthomyxoviridae*. There are three types of influenza viruses: A, B and C. Influenza A viruses are the most common form, which can spread in mammals and birds. The subtypes of influenza A are named by the types of surface proteins hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin and 11 known neuraminidases. Current seasonal influenza viruses found in human are mainly H1N1 and H3N2 subtypes. Influenza B viruses are usually found only in humans. They are not divided into subtypes, but can be further broken down into different strains. Circulating influenza viruses are highly variable each year, and both influenza A and B cause seasonal epidemics all over the world. Influenza C viruses give much milder symptoms, which do not cause epidemics.

All three types of viruses have similar genome structures. The genome comprises 8 segments, encoding 9-11 proteins, depending on the type. Influenza A encodes 11 proteins, which includes the surface proteins (hemagglutinin (HA) and Neuraminidase

(NA), the polymerase complex, nucleoprotein (NP), membrane proteins (M1 and M2), and other proteins (NS1, NS2, NEP). The polymerase complex is a heterotrimer composed of three subunits: polymerase acid (PA), polymerase basic 1 (PB1) and polymerase basic 2 (PB2). This polymerase is responsible for replication and transcription of the viral RNA in the nuclei of infected cells. The PA subunit contains the endonuclease active site. The endonuclease activity of the PA cleaves the cellular mRNA, which is then used by the PB1 subunit as a primer for the viral mRNA synthesis.

The most effective way to prevent the disease and/or severe outcomes from the illness is vaccination. However, vaccination comes with several limitations. First, influenza vaccine may be less effective in preventing illness among the elderly, and may only reduce severity of disease and incidence of complications and deaths. In addition, influenza vaccination is most effective when circulating viruses are well-matched with vaccine viruses, and the success of vaccination is largely dependent on the good prediction of the most prevalent virus type of the season. Rapid and continual evolution of influenza viral strains through antigenic drift, coupled with the short-lived nature of vaccine-induced immune responses to current influenza vaccines, means that vaccination with seasonally appropriate strains is required every year for prevention.

The current treatment of influenza uses either direct antiviral drugs, or medicines that reduce influenza-induced symptoms. There are two classes of influenza antiviral drugs available on the market: neuraminidase inhibitors and M2 channel inhibitors. Neuraminidase inhibitors oseltamivir or zanamivir are the primary antiviral agents recommended for the prevention and treatment of influenza. These are effective against both influenza type A and B viruses. Development of resistance to these antiviral drugs has been identified during treatment of seasonal influenza and in sporadic oseltamivir-resistant 2009 H1N1 virus, but the public health impact has been limited to date. M2 channel inhibitors, such as amantadine and rimantadine (adamantanes), are active against influenza A strains, but not influenza B strains. Adamantane resistance among circulating influenza A viruses increased rapidly worldwide beginning during 2003-2004. Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.

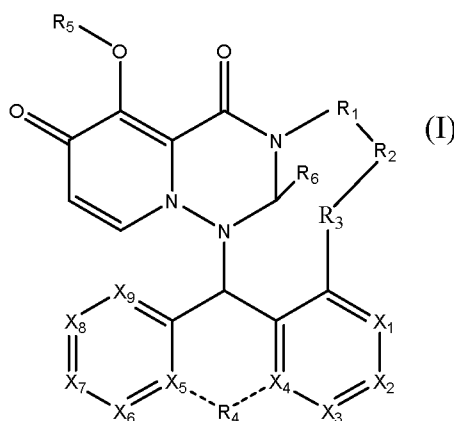
In 2009, the novel swine H1N1 strain caused an unexpected influenza pandemic as a result of reassortment of genes from human, pig, and bird's H1N1 viruses. This past pandemic, together with the ongoing circulation of highly pathogenic avian H5N1 strains and the recent emergence of the H7N9 virus, a new reassortant of avian origin isolated in China, and associated with severe respiratory disease with 40% of mortality, which

could potentially adapt for human-to-human transmission, highlighted the vulnerability of the world population to novel influenza strains. Although vaccination remains the main prophylactic strategy for controlling influenza infection, to bridge the period before a new vaccine becomes available and to treat the severe influenza cases, as well as to counter the problem of viral resistance, a wider choice of anti-influenza drugs is required. Development of new influenza antivirals has therefore again become a high priority and an unmet medical need.

SUMMARY OF THE INVENTION

The present invention provides macrocyclic pyridotriazine derivatives and the prodrugs thereof, the pharmaceutically acceptable salts and solvates thereof, having activity against influenza virus, in particular influenza A and B strains.

In one aspect, the present invention provides compounds of Formula (I)



and all possible stereoisomeric forms thereof, wherein:

R₁ is C, -CH₂-CH₂-O-, C₃₋₆cycloalkyl, oxetanyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo, oxo, CH₂-methoxy, C₁₋₄alkyl, C₁₋₆ cycloalkyl and tetrahydrofuran;

R₂ is C₁₋₆alkyl, C₁₋₆alkyl-O-, C₁₋₆alkyl-N-, C₂₋₆alkenyl, C₂₋₆alkenyl-O- or C₂₋₆alkenyl-N- optionally substituted by one or more substituents independently selected from halo, oxo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

or, R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

the dotted lines are each an optional bond;

- 5 R₄ is absent, -CH₂-CH₂-, -O-CH₂-, -S-CH₂-, S-(O)₂-CH₂ or cyclopropyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

R₅ is H, -C(=O)Y, -(CH₂)-O-(C=O)-Y, -(CH₂)-O-(C=O)-O-Y, -(CHCH₃)-O-(C=O)-Y, -(CHCH₃)-O-(C=O)-O-Y, -(CH₂)-O-(C=O)-NH-Y, -(CH₂)-O-(C=O)C(R₇)-NH-(R₈);

- 10 Y is C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, C₁₋₄alkyl-(O-R₇), C₁₋₄alkyl-N-(R₇)(R₈), R₇-O-R₈-O-CH₂;

and R₇ and R₈ are independently hydrogen or C₁₋₄alkyl;

R₆ is H, methyl or CH₂-O-CH₃;

and the pharmaceutically acceptable salts, polymorphs and solvates thereof.

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The invention also relates to a pharmaceutical composition comprising a therapeutically effective amount, in particular an anti-virally effective amount, of the compound of Formula (I) or a stereoisomeric forms thereof or a prodrug thereof, a pharmaceutically acceptable salt, solvate or polymorph thereof, and one or more pharmaceutically acceptable excipients, diluents or carriers.

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The invention further relates to a compound of Formula (I) or a stereoisomeric forms thereof or a prodrug thereof or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use as a medicament, in particular for use in the treatment or in the prevention of influenza virus infections, particularly influenza A and/or influenza B virus infections.

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Additionally, the invention relates to the use of a compound of Formula (I) or a stereoisomeric forms thereof or a prodrug thereof or a pharmaceutically acceptable salt, solvate or polymorph thereof, in combination with an additional antiviral for use in the treatment or prevention of influenza virus infections, particularly influenza A and/or influenza B virus infections.

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The invention also relates to a product comprising a compound of Formula (I) or a stereoisomeric forms thereof or a prodrug thereof or a pharmaceutically acceptable salt, solvate or polymorph thereof, and an additional pharmaceutical agent, in particular an additional antiviral, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of influenza virus infections, influenza A and/or influenza B virus infections.

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DETAILED DESCRIPTION OF THE INVENTION

Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

The term "about" has the meaning known to the person skilled in the art. In certain embodiments, the term "about" may be left out and the exact amount is meant. In other embodiments the term "about" means that the numerical following the term "about" is in the range of $\pm 15\%$, or of $\pm 10\%$, or of $\pm 5\%$, or of $\pm 1\%$, of said numerical value.

As used herein the term " C_{x-y} ", where x and y are integers, refers to the number of carbon atoms in a given group. Thus, a C_{1-6} alkyl group contains from 1 to 6 carbon atoms, a C_{1-4} alkyl group contains from 1 to 4 carbon atoms, a C_{1-3} alkyl group contains from 1 to 3 carbon atoms, a C_{3-6} cycloalkyl group contains from 3 to 6 carbon atoms, and so on.

The term "alkyl" refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon containing the specified number of carbon atoms.

The term "cycloalkyl" refers to a carbocyclic ring containing the specified number of carbon atoms including organic, inorganic and heterocycles.

The terms " C_2-C_6 alkenyl" and " C_2-C_8 alkenyl" used herein as a group or part of a group are meant to comprise straight or branched chain unsaturated hydrocarbon radicals having at least one double bond, and preferably having one double bond, and respectively from 2 to 6 and 2 to 8 carbon atoms such as ethenyl, propenyl, buten-1-yl, buten-2-yl, penten-1-yl, penten-2-yl, hexen-1-yl, hexen-2-yl, hexen-3-yl, 2-methylbuten-1-yl, hepten-1-yl, hepten-2-yl, hepten-3-yl, hepten-4-yl, 2-methylhexen-1-yl, octen-1-yl, octen-2-yl, octen-3-yl, octen-4-yl, 2-methylhepten-1-yl and the like.

The term "halo" or "halogen" is generic to fluoro, chloro, bromo and iodo.

The term "(=O)" or "oxo" forms a carbonyl moiety when attached to a carbon atom. It should be noted that an atom can only be substituted with an oxo group when the valency of that atom so permits.

It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable. Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated.

When any variable occurs more than one time in any constituent, each definition is independent.

The compounds of the present invention are represented herein in their neutral form, it should be clear that the charged form(s), as present in biological systems, and known to the skilled person, is/are also included within the scope of the present invention.

The term “prodrug” of a compound of the invention includes any compound that when administered to a biological system, generates the biologically active agent having the desired pharmacological effect, i.e. the antiviral activity, as a result of a biotransformation or chemical transformation (e.g. spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s)). Ideally the prodrug is pharmacologically inactive. General information on prodrugs may be found e.g. in Bundegaard, H. “Design of Prodrugs” p. 1-92, Elsevier, New York-Oxford (1985).

Several prodrug forming strategies are available in the field of antivirals and known to the skilled person. Such prodrug strategies have been reviewed, for instance, in Jones RJ and Bischofberger N, Antiviral Research 1995, 27, 1-17; Sofia, MJ, Antivir Chem Chemother 2011, 22, 23-49; Bobeck DR et al. Antiviral Therapy 2010, 15, 935-950; Sofia MJ, Adv Pharmacol 2013, 67, 39-73; Schultz C, Bioorg Med Chem 2003, 11, 885-898; Pertusati F et al. Antivir Chem Chemother 2012, 22, 181-203; Sofia MJ et al. J Med Chem 2012, 55(6), 2481-2531; Coats SJ et al. Antiviral Res 2014, 102, 119-147; Meier C and Balzarini J, Antiviral Res 2006, 71 (2-3), 282-292, incorporated by reference herein in their entirety.

Prodrugs may be prepared by modifying functional groups present on the compound in such a way that the modified functional groups are cleaved, *in vivo* when such prodrug is administered to a subject. The modifications typically are achieved by synthesising the

parent compound with a prodrug substituent. In general, prodrugs include compounds of the invention wherein a hydroxyl, amino or phosphate group is modified.

5 The term "polymorph" refers to the ability of the compound of the invention to exist in more than one form or crystal structure.

The term "optionally substituted" means that the atom or radical indicated in the expression using "optionally substituted" may or may not be substituted (this means substituted or unsubstituted respectively).

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The term "subject" as used herein, refers to a warm-blooded animal, preferably a mammal (e.g. cat, dog, primate or human), more preferably a human, who is or has been the object of treatment, observation or experiment.

15 The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁₋₇alkylamine, Cyclohexylamine, Triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

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The term "solvates" covers any pharmaceutically acceptable solvates that the compounds of Formula (I), as well as the prodrugs and the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates, e.g. ethanolates, propanolates, and the like.

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The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a

tissue system, animal or human that is being sought by a researcher, veterinarian, medicinal doctor or other clinician, which includes alleviation or reversal of the symptoms of the disease or disorder being treated.

- 5 The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

10 The term "treatment", as used herein, is intended to refer to all processes wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

15 The term "compounds of Formula (I)", or "the present compounds" or similar terms, it is meant to include the compounds of Formula (I), including the possible stereochemically isomeric forms, and their pharmaceutically acceptable salts and solvates.

20 As used herein, any chemical formula with bonds shown only as solid lines and not as solid or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. *R*, *S*) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

25 When a stereocenter is indicated with 'RS' this means that a racemic mixture was obtained at the indicated centre, unless otherwise indicated. The stereochemical configuration for centres in some compounds may be designated "*R*" or "*S*" when the mixture(s) was separated; for some compounds, the stereochemical configuration at indicated centres has been designated as "*R**", "*S**", "**R*" or "**S*" when the absolute stereochemistry is undetermined although the compound itself has been isolated as a single stereoisomer and is enantiomerically/diastereomerically pure.

30 "*E**", "*Z**", "**E*" or "**E*" when shown in a compound containing a double bond refer to a double bond for which the configuration is undetermined although the compound itself has been isolated as a single stereoisomer.

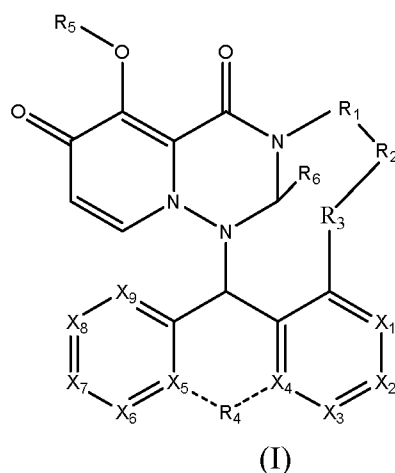
35 Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term "stereoisomerically pure" concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i.e. minimum 90% of one isomer and maximum

10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%, or of 98% up to 100%. The terms “enantiomerically pure” and “diastereomerically pure” should be understood in a similar way, but then having regard to the enantiomeric excess, and the diastereomeric excess, respectively, of the mixture in question.

- 10 Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphorsulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary layers. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound is synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of the compounds of Formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

In one embodiment, compounds of Formula (I) are provided wherein:



wherein:

R₁ is C, -CH₂-CH₂-O-, C₃₋₆cycloalkyl, oxetanyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo, oxo, CH₂-methoxy, C₁₋₄alkyl, C₁₋₆ cycloalkyl and tetrahydrofuran;

R₂ is C₁₋₆alkyl, C₁₋₆alkyl-O-, C₁₋₆alkyl-N-, C₂₋₆alkenyl, C₂₋₆alkenyl-O- or C₂₋₆alkenyl-N- optionally substituted by one or more substituents independently selected from halo, oxo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

or, R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

the dotted lines are each an optional bond;

R₄ is absent, -CH₂-CH₂-, -O-CH₂-, -S-CH₂-, S-(O)₂-CH₂ or cyclopropyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

R₅ can be a group that in vivo is capable of providing a compound of formula (I), wherein R₅ is H, -C(=O)Y, -(CH₂)-O-(C=O)-Y, -(CH₂)-O-(C=O)-O-Y, -(CHCH₃)-O-(C=O)-Y, -(CHCH₃)-O-(C=O)-O-Y, -(CH₂)-O-(C=O)-NH-Y, -(CH₂)-O-(C=O)C(R₇)-NH-(R₈);

Y is C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, C₁₋₄alkyl-(O-R₇), C₁₋₄alkyl-N-(R₇)(R₈), R₇-O-R₈-O-CH₂;

and R₇ and R₈ are independently hydrogen or C₁₋₄alkyl;

R₆ is H, methyl or CH₂-O-CH₃;

and the pharmaceutically acceptable salts, polymorphs and solvates thereof.

In one embodiment, compounds of Formula (I) are provided wherein

R₁ is C, -CH₂-CH₂-O-, C₃₋₆cycloalkyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo, oxo, CH₂-methoxy, C₁₋₄alkyl, and C₁₋₆ cycloalkyl;

R₂ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkenyl-O- or C₂₋₆alkenyl-N- optionally substituted by one or more substituents independently selected from halo, oxo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

or, R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

R₄ is absent, -CH₂-CH₂- or -S-CH₂- optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

R₅ is H, -C(=O)Y, -(CH₂)-O-(C=O)-Y, -(CH₂)-O-(C=O)-O-Y, -(CHCH₃)-O-(C=O)-Y, -(CHCH₃)-O-(C=O)-O-Y, -(CH₂)-O-(C=O)-NH-Y, -(CH₂)-O-(C=O)C(R₇)-NH-(R₈);

Y is C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, C₁₋₄alkyl-(O-R₇), C₁₋₄alkyl-N-(R₇)(R₈), R₇-O-R₈-O-CH₂;

and R₇ and R₈ are independently hydrogen or C₁₋₄alkyl;

R₆ is H or methyl.

In one embodiment, compounds of Formula (I) are provided wherein

R₁ is C, C₃₋₆cycloalkyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo, C₁₋₄alkyl, and C₁₋₆ cycloalkyl;

R₂ is C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo and methyl;

or, R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

R₄ is absent or -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ is H; and

R₆ is H or methyl.

In one embodiment, compounds of Formula (I) are provided wherein

R₁ is C, C₃₋₆cycloalkyl or C₁₋₃alkyl-cyclopropyl, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

R₂ is C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

R₄ is absent or -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ is H; and

R₆ is H or methyl.

In one embodiment, compounds of Formula (I) are provided wherein

R₁ is C, C₃₋₆cycloalkyl or C₁₋₃alkyl-cyclopropyl, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

R₂ is C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo and methyl;

X₁ to X₉ are each C which is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl or halogen;

R₄ is absent or -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ is H; and

R₆ is H or methyl.

In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₁ is C, C₃₋₆cycloalkyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₂ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkenyl-O- or C₂₋₆alkenyl-N- optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₃ is C optionally substituted by one or more substituents independently selected from halo and methyl.

In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₃ is O.

5 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo and methyl.

10 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein X₁ to X₉ are each N.

15 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein X₁ to X₉ are each C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl or halogen.

20 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₄ is absent.

25 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₄ is -CH₂-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

30 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₄ is -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl.

In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₅ is H.

35 In an embodiment, the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein R₆ is H.

In one embodiment, compounds of Formula (I) are provided wherein:

R₁ is C optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

R₂ is C₂₋₆alkenyl;

R₃ is O;

- 5 X₁ to X₉ are each C which is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl or halogen;

R₄ is absent;

R₅ and R₆ are each H.

- 10 In one embodiment, compounds of Formula (I) are provided wherein

R₁ is C₃₋₆cycloalkyl;

R₂ is C₂₋₆alkenyl;

R₃ is O;

X₁ to X₉ are each C which is optionally substituted by one or more substituents

- 15 independently selected from C₁₋₄alkyl or halogen;

R₄ is absent;

R₅ and R₆ are each H.

In one embodiment, compounds of Formula (I) are provided wherein

- 20 R₁ is C, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

R₂ is C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

R₃ is O;

- 25 X₁ to X₉ are each C which is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl or halogen;

R₄ is -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ and R₆ are each H.

30

In one embodiment, compounds of Formula (I) are provided wherein

R₁ is C₃₋₆cycloalkyl;

R₂ is C₁₋₆alkyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

- 35 R₃ is O;

X₁ to X₉ are each C which is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl or halogen;

R₄ is -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

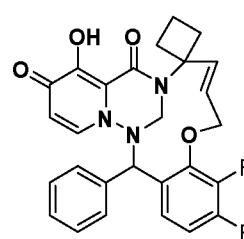
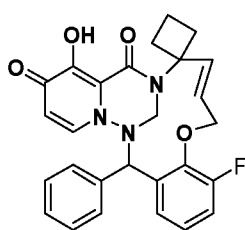
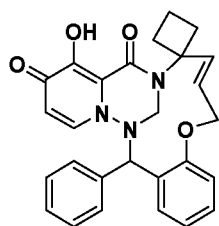
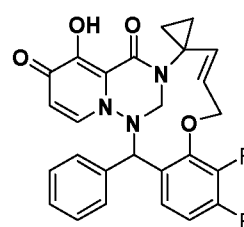
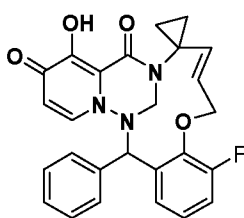
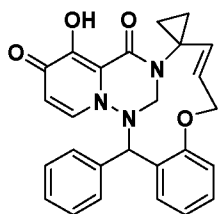
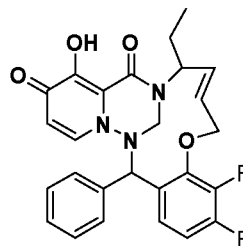
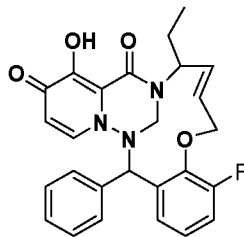
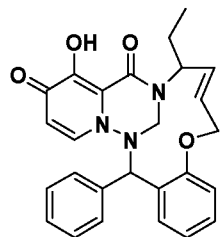
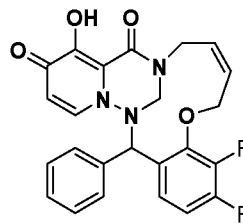
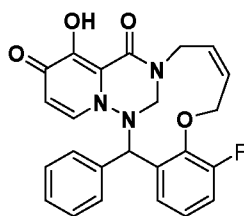
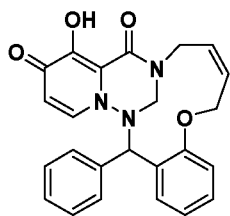
R₅ and R₆ are each H.

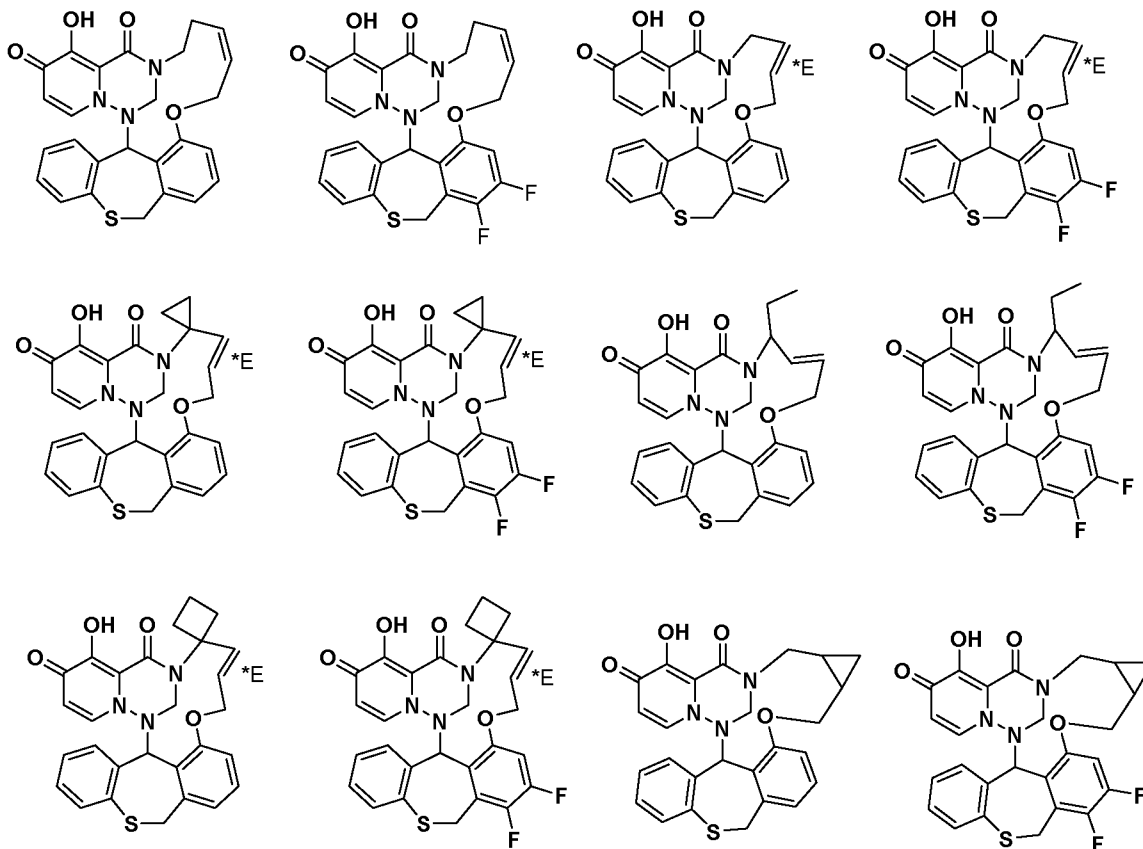
- 5 In one embodiment, compounds of Formula (I) are provided wherein
R₁ is C₁₋₃alkyl-cyclopropyl optionally substituted by one or more substituents independently selected from halo and C₁₋₄alkyl;
R₂ is C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;
10 R₃ is O;
X₁ to X₉ are each C which is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl or halogen;
R₄ is -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;
15 R₅ and R₆ are each H.

- In an embodiment, the present invention relates to those compounds of Formula (I) and the prodrugs thereof, the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments wherein at least 1,
20 2, 3, 4 or 5 of X₁ to X₉ is N.

All possible combinations of the above-indicated embodiments are considered to be embraced within the scope of this invention.

- 25 Of interest are the compounds listed below as well as the pharmaceutically acceptable acid addition salts of the following compounds:





Synthetic approaches

- 5 The compound of Formula (I) may be prepared by the methods described below, using synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of skilled in the art. The starting materials used herein are commercially available or may be prepared by routine methods known in the art such as those methods disclosed in standard reference books. Preferred methods
- 10 include, but are not limited to, those described below.

- During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W.
- 15 Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, which are hereby incorporated by reference.

- Compounds of Formula (I), or their pharmaceutically acceptable salts, can be prepared according to the reaction schemes discussed herein below. Unless otherwise indicated,
- 20 the substituents in the schemes are defined as above. Isolation and purification of the

products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

LC/MS methods

5

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

10

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

15

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc...). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

20

25

Hereinafter, "SQD" means Single Quadrupole Detector, "MSD" Mass Selective Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "DAD" Diode Array Detector, "HSS" High Strength silica.

LCMS Method codes (Flow expressed in mL/min, column temperature (T) in °C; Run time in minutes)

30

Method code	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time (min)
LC-A -	Waters: Acquity® UPLC® - DAD- Quattro Micro™	Waters: BEH C18 (1.7µm, 2.1x100mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 mL/min ----- 40°C	6.2

Method code	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time (min)
LC-B -	Waters: Acquity® H-Class - DAD and SQD2TM	Waters BEH® C18 (1.7µm, 2.1x100mm)	A: CH ₃ COONH ₄ 7mM 95%/ CH ₃ CN 5% B: CH ₃ CN	84.2% A/15.8% B, to 10.5% A in 2.18 min, held for 1.96 min, back to 84.2% A/15.8% B in 0.73 min, held for 0.49 min.	0.343 mL/min ----- 40°C	6.1
LC-C -	Waters: Acquity UPLC® - DAD and Quattro Micro™	YMC Triart C18 ExRS: (1.9µm, 2.1x100mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	85% A for 0.5min, to 15% A in 2.5min, held for 1.6min, back to 85% A in 0.8min, held for 0.8min.	0.343 mL/min ----- 40°C	6.2
LC-D -	Shimadzu LCMS- 2020	Shimadzu CORTECS C18 (2.7µm, 2.1x50mm)	A: H ₂ O/0.05%TFA, B: CH ₃ CN/0.05% TFA	95% A for 0.01min, to 0% A in 1.99min, held for 0.8min, back to 95% A in 0.1min, held for 0.1 or 0.25min.	1, 1.2 or 1.5 mL/min ----- 40°C	3 or 5.2
LC-E	Serie 1200 Agilent Technology	ZORBAX SB C18 1.8µM (50 x 2.1 mm)	A: H ₂ O + 0.1% HCO ₂ H Methanol + 0.1% HCO ₂ H	0 min : 95/5 2.5 min : 0/100 5 min: 0/100	0.8mL/min ----- 40°C	5
LC-F	Serie 1200 Agilent Technology	ZORBAX SB C18 1.8µM (50 x 2.1 mm)	A: H ₂ O + 0.1% HCO ₂ H Methanol + 0.1% HCO ₂ H	0 min : 60/40 10 min : 0/100 14 min: 0/100	0.8mL/min ----- 40°C	14
LC-G	Waters: Acquity UPLC® - DAD and Quattro Micro™	Peek-YMC Triart C18 ExRS: (1.9µm, 2.1x100mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	85% A for 0.5min, to 15% A in 2.5min, held for 1.6min, back to 85% A in 0.8min, held for 0.8min.	0.343 mL/min ----- 40°C	6.2

HPLC methods

General procedure

The HPLC measurement was performed using Analytical system from Waters comprises
5 a modules pump-autosampler alliance 2695 and a diode array detector996. Data

acquisition and reprocess was performed with a Waters-Micromass MassLynx data system.

Method code	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
Method HPLC-A	Chiralpak IG 250*4.6mm 5µm	EtOH +(0.1% TFA v/v)	100%	1mL/min ----- 25°C	15min
Method HPLC-B	Chiralpak AZ-H 250*4.6mm 5µm	EtOH +(0.1% TFA v/v)	100%	1mL/min ----- 25°C	15min

5 *SFCMS-Method:*

General procedure

The SFC measurement was performed using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO₂) and modifier, an autosampler, a column oven, a diode array detector equipped with a high-pressure flow cell standing up to 400 bars. If configured with a Mass Spectrometer (MS) the flow from the column was brought to the (MS). It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

- 15 Analytical SFC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes, Backpressure (BPR) in bars.

Method code	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
Method SFC-A	Daicel Chiralcel® OJ-3 column (3 µm, 100 x 4.6 mm)	A:CO ₂ B: MeOH	20% B hold 3 min,	3.5 ----- 35	3 ----- 103
Method SFC-B	Daicel Chiralcel® OJ-3 column (3 µm, 100 x 4.6 mm)	A:CO ₂ B: MeOH + 0.3% IprNH ₂	20% B hold 3 min,	3.5 ----- 35	3 ----- 103
Method SFC-C	Daicel Chiralcel® OJ-3 column (3 µm, 100 x 4.6 mm)	A:CO ₂ B: MeOH + 0.3% IprNH ₂	15% B hold 3 min,	3.5 ----- 35	3 ----- 103

Melting Points

Values are either peak values or melt ranges, and are obtained with experimental uncertainties that are commonly associated with this analytical method.

5 DSC823e (indicated as DSC)

For a number of compounds, melting points were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 10°C/minute. Maximum temperature was 300°C.

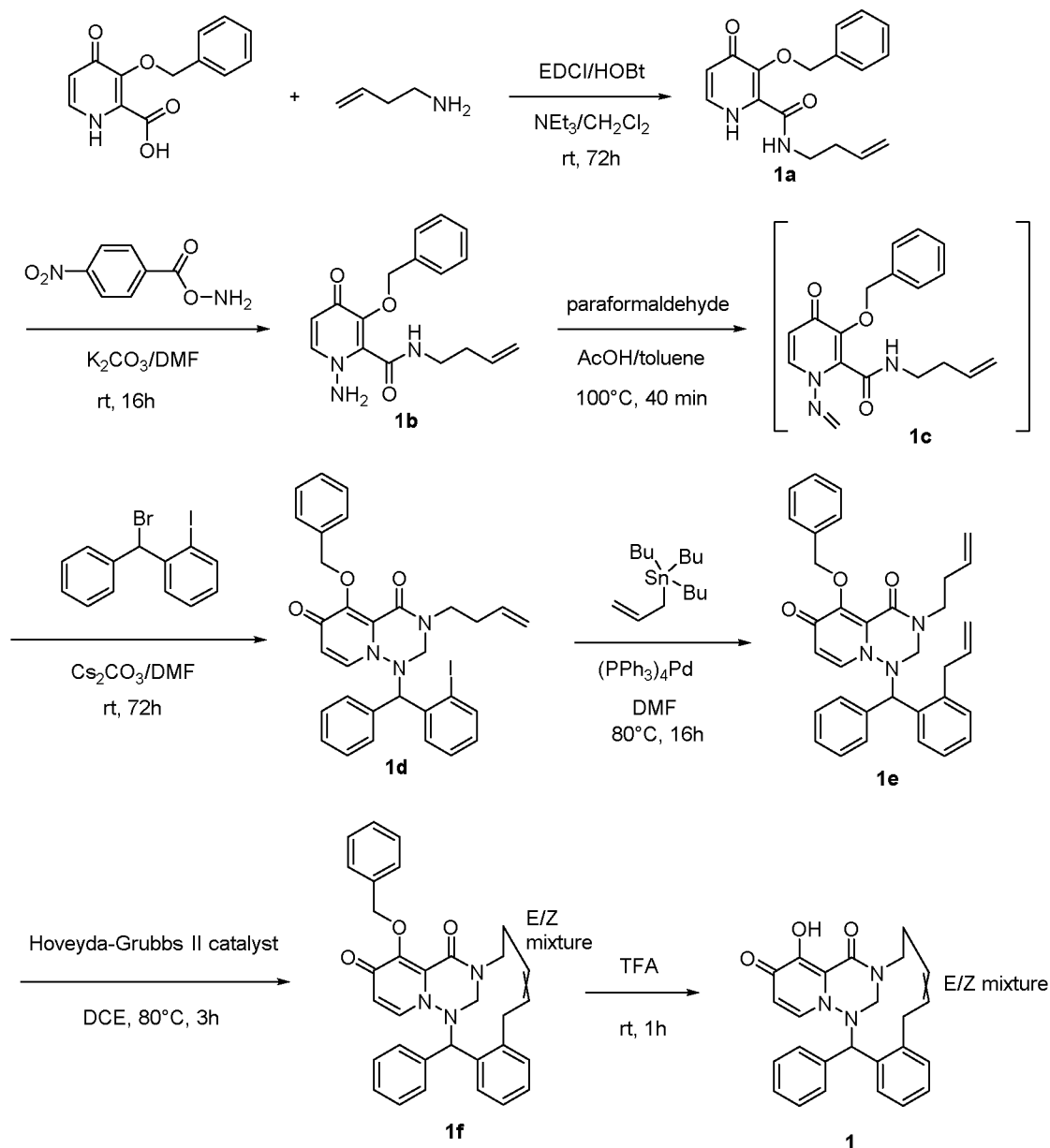
10 Optical Rotations:

Optical rotations were measured on a Perkin-Elmer 341 polarimeter with a sodium lamp and reported as follows: $[\alpha]^\circ (\lambda, c \text{ g/100 mL, solvent, } T^\circ\text{C})$.

$[\alpha]_\lambda^T = (100\alpha) / (l \times c)$: where l is the path length in dm and c is the concentration in g/100 ml for a sample at a temperature T (°C) and a wavelength λ (in nm). If the wavelength of light used is 589 nm (the sodium D line), then the symbol D might be used instead. The sign of the rotation (+ or -) should always be given. When using this equation, the concentration and solvent are always provided in parentheses after the rotation. The rotation is reported using degrees and no units of concentration are given (it is assumed to be g/100 ml).

20 EXAMPLES**Preparation of compounds according to the invention**

25 Example 1: synthesis of 4-hydroxy-16-phenyl-7,8,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound 1).



Synthesis of intermediate **1a**:

At 10°C , NEt_3 (28 mL, 0.20 mol) was added to a solution of 3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxylic acid [CAS 119736-17-3] (10 g, 41 mmol), but-3-en-1-amine [CAS 2524-49-4] (4.8 mL, 53 mmol), EDCI (12 g, 61 mmol) and HOBt (8.3 g, 61 mmol) in CH_2Cl_2 (250 mL). The mixture was stirred at rt for 72 h. The mixture was poured into a mixture of water and K_2CO_3 10% in water, and was extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 , filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (30 μm , 300 g, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ from 100/0 to 96/4). The pure fractions were collected and concentrated under reduced pressure to give 3-(benzyloxy)-*N*-(but-3-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1a**, 4.6 g).

Synthesis of intermediate 1b:

To a DMF (240 mL) solution of 3-(benzyloxy)-*N*-(but-3-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1a**, 4.6 g, 15 mmol) was suspended K₂CO₃ (6.4 g, 46 mmol). The suspension was stirred for 5 min at rt. *O*-(4-nitrobenzoyl)hydroxylamine [CAS 35657-36-4] (4.2 g, 23 mmol) was added and the mixture was stirred at rt for 16 h. H₂O was added and the mixture was extracted five times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 µm, 120 g, CH₂Cl₂/MeOH from 100/0 to 95/5) to give 1-amino-3-(benzyloxy)-*N*-(but-3-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1b**, 3.2 g).

Synthesis of intermediate 1c:

A suspension of 1-amino-3-(benzyloxy)-*N*-(but-3-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1b**, 620 mg, 2.0 mmol) and paraformaldehyde (59 mg, 2.0 mmol) in dry toluene (21 mL) and AcOH (ten drops) was stirred at 100°C for 40 min. The mixture was cooled down to rt and concentrated under reduced pressure to give 3-(benzyloxy)-*N*-(but-3-en-1-yl)-1-(methyleamino)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1c**, 643 mg), which was used as such in the next step.

Synthesis of intermediate 1d:

Under N₂, 3-(benzyloxy)-*N*-(but-3-en-1-yl)-1-(methyleamino)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1c**, 640 mg, 2.0 mmol) was taken up in DMF (14 mL) and Cs₂CO₃ (3.2 g, 9.8 mmol) was added at 0°C. The reaction was stirred for 1 h at 0°C. Then 1-(bromo(phenyl)methyl)-2-iodobenzene [CAS 1339630-17-9] (1.1 g, 2.9 mmol) was added and the reaction mixture was stirred at rt for 72 h. EtOAc was added and the mixture was washed 5 times with brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 µm, 24 g, CH₂Cl₂/MeOH from 100/0 to 98/2). The pure fractions were collected and evaporated to dryness to give 5-(benzyloxy)-3-(but-3-en-1-yl)-1-((2-iodophenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **1d**, 0.45 g).

Synthesis of intermediate 1e:

To a solution of 5-(benzyloxy)-3-(but-3-en-1-yl)-1-((2-iodophenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **1d**, 0.45 g, 0.73 mmol) and allyltri-*N*-butyltin (0.27 mL, 0.88 mmol) in degassed DMF (5.6 mL) under N₂ was added (PPh₃)₄Pd (42 mg, 0.036 mmol). The mixture was stirred at 80°C for 16 h. The

mixture was partitioned between EtOAc and brine, the organic layer was separated, washed five times with brine, dried and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μ m, 24 g, CH₂Cl₂/MeOH from 100/0 to 97/3) to give 1-((2-allylphenyl)(phenyl)methyl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **1e**, 350 mg).

Synthesis of intermediate **1f**:

A solution of 1-((2-allylphenyl)(phenyl)methyl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **1e**, 350 mg, 0.66 mmol) and Hoveyda-Grubbs catalyst 2nd generation [CAS 301224-40-8] (83 mg, 0.13 mmol) in dry DCE (52 mL) was stirred at 80°C for 3 h. SiliaMetS[®] DMT (0.86 g, 0.53 mmol) was added and the mixture was stirred at rt overnight. The reaction mixture was filtered through celite[®] and the filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 μ m, 12 g, CH₂Cl₂/CH₃OH 100/0 to 97/3) to give 4-(benzyloxy)-16-phenyl-7,8,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **1f**, *Z/E* mixture, 230 mg), which was used as such in the next step.

Synthesis of Compound **1**:

TFA (0.76 mL) was added to 4-(benzyloxy)-16-phenyl-7,8,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **1f**, 50 mg, 0.099 mmol). The mixture was stirred at rt for 1h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μ m, 4 g, CH₂Cl₂/MeOH from 99/1 to 95/5) to give, after freeze drying in CH₃CN/water, 4-hydroxy-16-phenyl-7,8,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **1**, *Z/E* mixture, 26 mg).

Compound **1**:

major isomer (75%)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.17 (br d, *J*=12.6 Hz, 1H) 2.60 - 2.74 (m, 1H) 2.79 (td, *J*=13.0, 3.6 Hz, 1H) 2.96 - 3.03 (m, 1H) 3.11 (br d, *J*=17.3 Hz, 1H) 3.69 (br dd, *J*=13.6, 4.4 Hz, 1H) 4.11 (d, *J*=13.2 Hz, 1H) 4.89 - 5.06 (m, 2H) 5.33 (d, *J*=7.6 Hz, 1H) 5.79 (s, 1H) 6.12 - 6.27 (m, 1H) 6.81 - 7.32 (m, 7H) 7.37 - 7.58 (m, 2H) 8.08 (d, *J*=7.6 Hz, 1H) 9.59 - 12.93 (m, 1H)

minor isomer (25%)

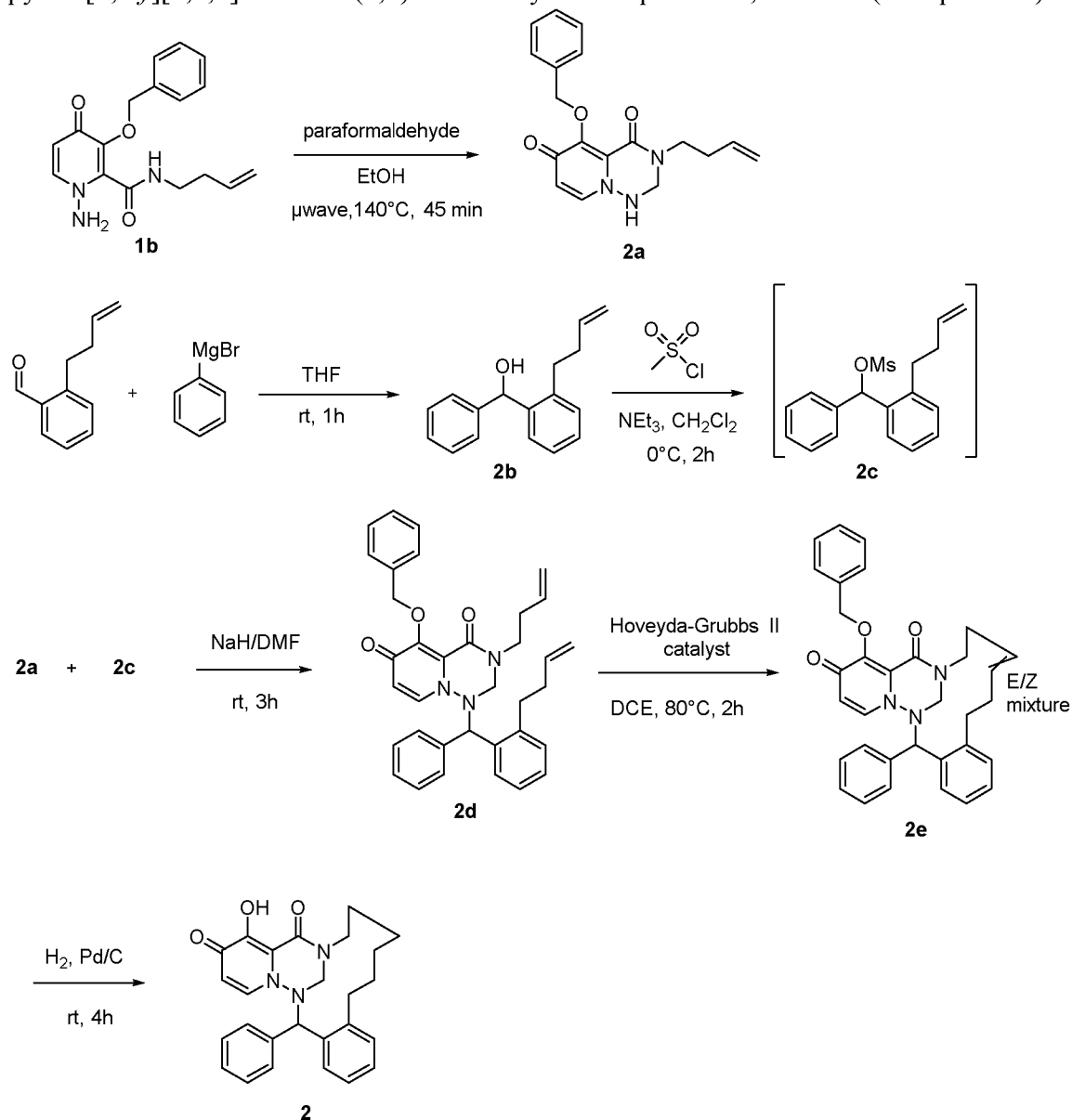
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.17 (br d, *J*=12.6 Hz, 1H) 2.60 - 2.74 (m, 1H) 2.79 (td, *J*=13.0, 3.6 Hz, 1H) 2.96 - 3.03 (m, 1H) 3.11 (br d, *J*=17.3 Hz, 1H) 3.69 (br dd,

$J=13.6, 4.4$ Hz, 1H) 3.98 - 4.07 (m, 1H) 4.36 (br d, $J=13.2$ Hz, 1H) 4.89 - 5.06 (m, 1H) 5.38 - 5.68 (m, 3H) 6.81 - 7.32 (m, 7H) 7.37 - 7.58 (m, 2H) 7.94 (br d, $J=7.3$ Hz, 1H) 9.59 - 12.93 (m, 1H)

LC-MS (method LC-A): R_t 2.68 min, MH^+ 414

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Example 2: synthesis of 15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphane-14,16-dione (Compound **2**).



10 Synthesis of intermediate 2a:

The reaction was split into two equal parts. 1-amino-3-(benzyloxy)-*N*-(but-3-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **1b**, 40.0 g, 127.65 mmol) was solubilized in EtOH (612 mL) in a warm water bath (50°C). Paraformaldehyde (4.22 g,

140.42 mmol) was added and the resulting mixture was stirred at 140°C for 45 min (3 min as ramp time, 600 rpm as stirring speed) in an Anton-Parr microwave oven (1700 W max power). The mixture was concentrated under vacuum (water bath at 35°C). The residue was taken up with a minimum amount of CH₃CN. The precipitate was filtered off and dried under vacuum to give a first batch of 5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1H-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **2a**, 30.7 g). The filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 μm, 330 g, CH₂Cl₂/CH₃OH: 98/2 to 95/5). The pure fractions were collected and evaporated to dryness to give a second batch of intermediate **2a** (3.7 g).

Synthesis of intermediate **2b**:

At 0°C under a N₂ flow, phenyl-magnesium bromide [CAS 100-58-3] (35 mL, 34.89 mmol) was added dropwise to a solution of 2-(but-3-en-1-yl)benzaldehyde [CAS 70576-29-3] (4.3 g, 26.84 mmol) in THF (30 mL). The mixture was stirred under N₂ at rt for 1 h. The reaction was quenched at 0°C with a saturated aqueous solution of NH₄Cl and the aqueous phase was extracted with EtOAc. The organic extracts were combined and dried over MgSO₄, filtered and concentrated under reduced pressure to give (2-(but-3-en-1-yl)phenyl)(phenyl)methanol (intermediate **2b**, 4.2 g).

Synthesis of intermediate **2c**:

At 0°C under a N₂ flow, methanesulfonyl chloride (974 μL, 12.59 mmol) was added dropwise to a solution of (2-(but-3-en-1-yl)phenyl)(phenyl)methanol (intermediate **2b**, 1.5 g, 6.29 mmol) and NEt₃ (2.62 mL, 18.8 mmol) in CH₂Cl₂ (30 mL). The mixture was stirred at 0°C for 2 h. Water was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give (2-(but-3-en-1-yl)phenyl)(phenyl)methyl methanesulfonate (intermediate **2c**, 1.80 g), which was used as such in the next step.

Synthesis of intermediate **2d**:

At 0°C, under a N₂ flow, NaH (60% dispersion in oil, 145 mg, 3.78 mmol) was added to a solution of 5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1H-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **2a**, 820 mg, 2.52 mmol) in DMF (10 mL). The mixture was stirred at 0°C for 30 min (the mixture turned red), then a solution of (2-(but-3-en-1-yl)phenyl)(phenyl)methyl methanesulfonate (intermediate **2c**, 1.6 g, 5.04 mmol) in DMF (6 mL) was added. The resulting mixture was stirred at rt for 3 h (reaction mixture turned yellow). The mixture was quenched with ice and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and concentrated under reduced

pressure. Purification was carried out by flash chromatography over silica gel (15-40 μ m, 80 g, CH₂Cl₂/CH₃OH:100/0 to 97/3). The pure fractions were collected and concentrated under reduced pressure to give 5-(benzyloxy)-3-(but-3-en-1-yl)-1-((2-(but-3-en-1-yl)phenyl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione

5 (intermediate **2d**, 460 mg).

Synthesis of intermediate **2e**:

Synthesized using the procedure described for intermediate **1f** yielding 15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (intermediate **2e**, undefined *E/Z* mixture, 305 mg).

Synthesis of Compound **2**:

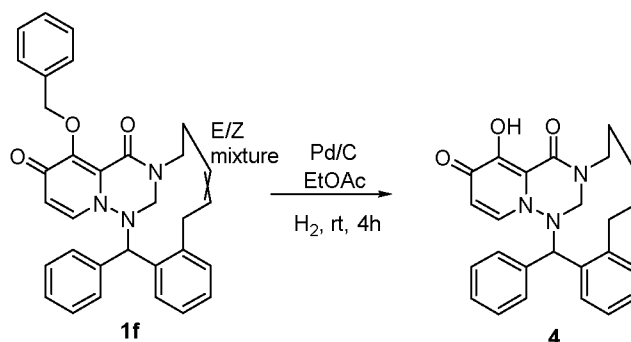
Under an atmospheric pressure of H₂, 15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (intermediate **2e**, 60 mg, 0.116 mmol) and Pd/C (10%) (61.7 mg, 0.058 mmol) in EtOAc (4 mL) were stirred at rt for 4 h. The catalyst was removed by filtration through a pad of celite[®]. The celite[®] was washed with EtOAc and the filtrate was concentrated under reduced pressure (45 mg). The compound was crystallized from CH₃OH/Et₂O, the precipitate was filtered off and dried to give 15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclonaphane-14,16-dione (Compound **2**, 32 mg).

Compound **2**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.99 - 1.07 (m, 1 H) 1.21 (br t, *J*=11.2 Hz, 1 H) 1.30 - 1.44 (m, 2 H) 1.70 - 1.81 (m, 2 H) 1.82 - 1.93 (m, 1 H) 2.27 - 2.35 (m, 1 H) 2.57 - 2.69 (m, 1 H) 2.94 (br t, *J*=10.7 Hz, 1 H) 3.72 (br d, *J*=13.2 Hz, 1 H) 4.40 (d, *J*=12.9 Hz, 1 H) 5.14 (d, *J*=13.2 Hz, 1 H) 5.40 (d, *J*=7.6 Hz, 1 H) 5.93 (s, 1 H) 7.21 (br dd, *J*=17.8, 9.9 Hz, 7 H) 7.30 - 7.36 (m, 1 H) 7.38 - 7.46 (m, 1 H) 8.16 (d, *J*=7.3 Hz, 1 H) 11.74 (br s, 1 H) (1 proton under DMSO peak)

LC-MS (method LC-A): R_t 2.93 min, MH⁺ 430

Example 4: synthesis of 4-hydroxy-16-phenyl-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **4**).



Synthesis of Compound 4:

Under an atmospheric pressure of H₂, 4-(benzyloxy)-16-phenyl-7,8,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **1f**, 30 mg, 0.060 mmol) and Pd/C (10%) (32 mg, 0.030 mmol) in EtOAc (1.8 mL) were stirred at rt for 4 h. The catalyst was removed by filtration through a pad of celite[®]. The celite[®] was washed with EtOAc and the filtrate was concentrated under reduced pressure to give, after freeze drying in CH₃CN/water, 4-hydroxy-16-phenyl-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **4**, 12 mg).

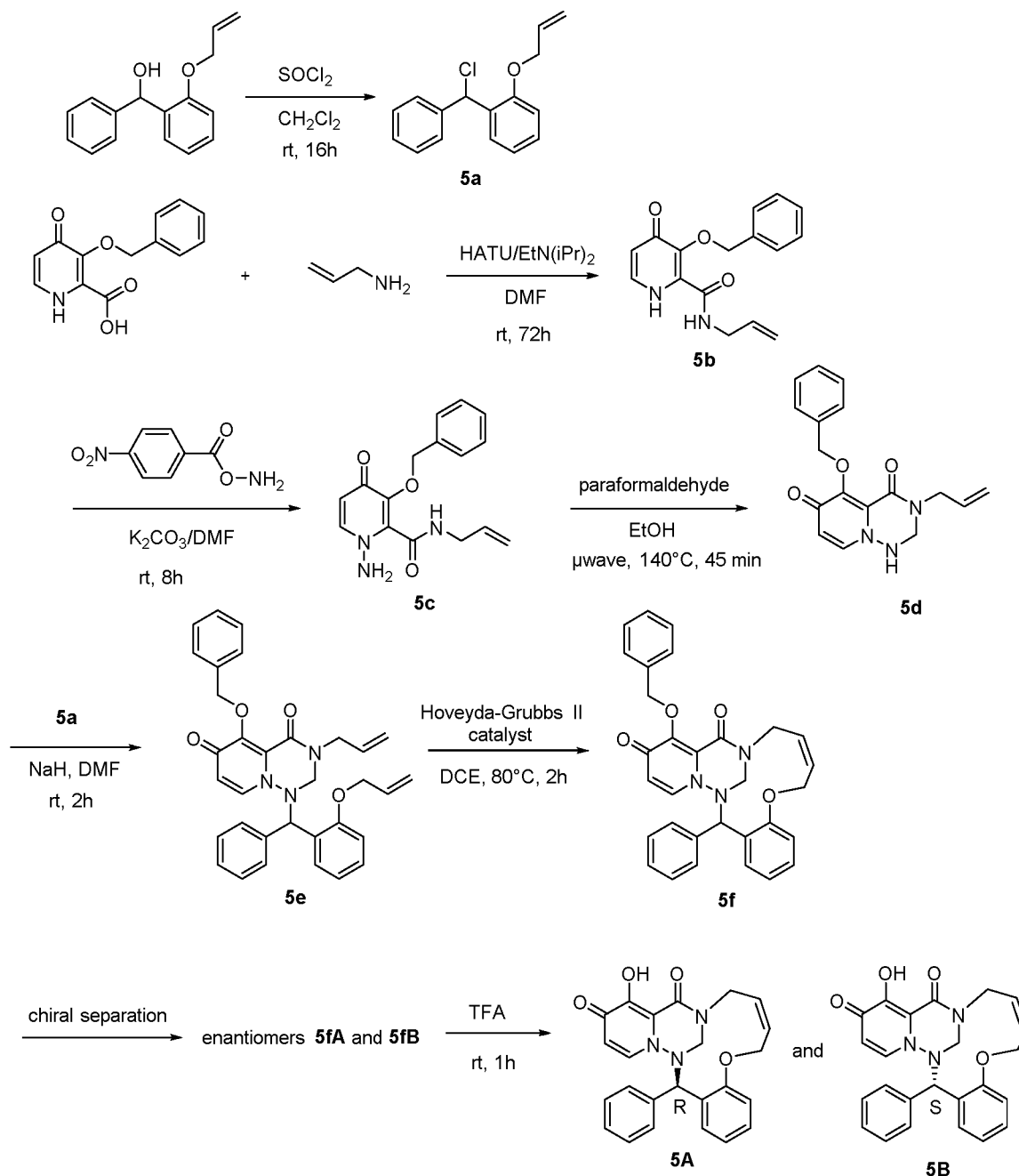
Compound 4:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.70 - 0.84 (m, 1 H) 1.28 - 1.40 (m, 1 H) 1.40 - 1.62 (m, 2 H) 1.65 - 1.84 (m, 1 H) 1.96 - 2.13 (m, 1 H) 2.54 - 2.58 (m, 1 H) 2.59 - 2.72 (m, 2 H) 3.90 - 4.12 (m, 1 H) 4.27 - 4.49 (m, 1 H) 5.08 (d, *J*=13.9 Hz, 1 H) 5.53 (d, *J*=7.9 Hz, 1 H) 5.61 (s, 1 H) 7.03 (d, *J*=7.6 Hz, 1 H) 7.17 - 7.47 (m, 8 H) 8.00 (d, *J*=7.3 Hz, 1 H)

LC-MS (method LC-A): R_t 2.76 min, MH^+ 416

Example 5: synthesis of (18*R,Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **5A**) and (18*S,Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **5B**)

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Synthesis of intermediate 5a:

Thionyl chloride (2 mL, 27.46 mmol) was added dropwise to a solution of (2-(allyloxy)phenyl)(phenyl)methanol [CAS 1159707-76-2 (5.5 g, 27.89 mmol) in CH_2Cl_2 (56 mL) at 5°C . The mixture was stirred at 5°C for 1 h and at rt for 16 h. The mixture was concentrated to dryness and co-evaporated with toluene to give 1-(allyloxy)-2-(chloro(phenyl)methyl)benzene (intermediate **5a**, 5.9 g), which was used as such in the next step.

Synthesis of intermediate 5b:

Under N₂, a mixture of 3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxylic acid [CAS 119736-17-3] (20 g, 73 mmol, 90% pure), allylamine (6.6 mL, 88 mmol), HATU (42 g, 110 mmol) and *N,N*-diisopropylethylamine (36 mL, 220 mmol) in DMF (284 mL) was stirred at rt for 72 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The mixture was washed 5 times with brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 µm, 300 g, dry loading, CH₂Cl₂/MeOH from 100/0 to 97/3). The pure fractions were collected and evaporated to dryness to give *N*-allyl-3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **5b**, 16 g).

Synthesis of intermediate 5c:

To a solution of *N*-allyl-3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **5b**, 13.1 g, 46.08 mmol) in DMF (250 mL) was suspended K₂CO₃ (19.1 g, 138.22 mmol). The reaction was stirred 5 min at rt. *O*-(4-nitrobenzoyl)hydroxylamine [CAS 35657-36-4] (12.6 g, 69.11 mmol) was added and the mixture was stirred at rt for 8 h. Water was added and the mixture was extracted five times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was taken up with CH₂Cl₂ and the precipitate was filtered off to give *N*-allyl-1-amino-3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **5c**, 11.5 g).

Synthesis of intermediate 5d:

N-allyl-1-amino-3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **5c**, 11.5 g, 38.42 mmol) was solubilized in EtOH (185 mL) using a warm water bath (50°C). *Para*formaldehyde (1.27 g, 42.26 mmol) was added and the resulting mixture was stirred at 140°C for 45 min (3 min as ramp time, 600 rpm as stirring speed) in an Anton-Parr microwave oven (1700 W max power). The mixture was concentrated under vacuum (water bath below 35°C). The residue was taken up with the minimum amount of CH₃CN. The precipitate was filtered off and dried under vacuum to give a first batch of 3-allyl-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **5d**, 6.71 g). The filtrate was concentrated under reduced pressure (5.3 g) and was combined with another reaction (3 g) to be further purified. Purification was carried out by flash chromatography over silica gel (30 µm, 80 g, mobile phase CH₂Cl₂/MeOH from 100/0 to 95/5) yielding another batch of intermediate **5d** (5 g).

Synthesis of intermediate 5e:

Under nitrogen, 3-allyl-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **5d**, 5.0 g, 16.06 mmol) was solubilized in DMF (80 mL) and NaH (960 mg, 24.09 mmol) was added at 0°C. The mixture was stirred for 30 min at 0°C. Then a solution of 1-(allyloxy)-2-(chloro(phenyl)methyl)benzene (intermediate **5a**, 6.0 g, 23.19 mmol) in DMF (20 mL) was added and the mixture was stirred at rt for 2 h. EtOAc was added and the mixture was washed with water. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 µm, 220 g, CH₂Cl₂/CH₃OH 100/0 to 97/3). The pure fractions were collected and evaporated to dryness to give 3-allyl-1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **5e**, 7.72 g).

Synthesis of intermediate 5f:

A degassed solution of 3-allyl-1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **5e**, 2.0 g, 3.65 mmol) and Hoveyda-Grubbs catalyst 2nd generation (470 mg, 0.75 mmol) in dry DCE (270 mL) was stirred at 80°C for 2 h. SiliaMetS[®] DMT (9.83 g, 6.0 mmol) was added and the mixture was stirred at rt for 16 h. The reaction mixture was filtered through a pad of celite[®]. The celite[®] was washed with CH₂Cl₂ and the filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (20-45 µm, 80 g, CH₂Cl₂/CH₃OH 100/0 to 96/4) to give (*Z*)-12-(benzyloxy)-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **5f**, *Z* isomer, 395 mg). This batch was combined with another one (409 mg) and the enantiomers were separated via chiral SFC (Stationary phase: Chiralcel[®] OD-H 5 µm 250 x 30mm, Mobile phase: 60% CO₂, 40% EtOH) to give 314 mg of the first eluted enantiomer and 378 mg of the second eluted enantiomer. Each enantiomer was further purified via achiral SFC (Stationary phase: NH₂ 5 µm 150 x 30 mm, Mobile phase: 80% CO₂, 20% EtOH) to give 137 mg of enantiomer **5fA** and 146 mg of enantiomer **5fB**.

Synthesis of Compound 5A:

TFA (2.1 mL) was added to the enantiomer **5fA** (137 mg, 0.27 mmol). The mixture was stirred at rt for 1 h and was then concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 µm, 4 g, CH₂Cl₂/MeOH from 99/1 to 95/5) to give, after freeze drying in CH₃CN/water, (18*R,Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **5A**, 87 mg).

Synthesis of Compound 5B:

TFA (2.2 mL) was added to the enantiomer **5fB** (146 mg, 0.29 mmol). The mixture was stirred at rt for 1 h and was then concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μ m, 4 g, CH₂Cl₂/MeOH from 99/1 to 95/5) to give, after freeze drying in CH₃CN/water, (18*S,Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **5B**, 90 mg).

Compound 5A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.19 (br dd, *J*=13.9, 8.3 Hz, 1 H) 4.08 - 4.47 (m, 2 H) 4.65 - 4.90 (m, 2 H) 5.11 (br d, *J*=13.6 Hz, 1 H) 5.31 (s, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.80-5.91 (m, 1 H) 6.04 - 6.32 (m, 1 H) 6.98 - 7.29 (m, 7 H) 7.29 - 7.49 (m, 2 H) 8.09 (br d, *J*=7.1 Hz, 1 H)

LC/MS (method LC-B): *R*_t 2.26 min, MH⁺ 416

$[\alpha]_D^{20}$: -708.58° (c 0.303, DMF)

Chiral HPLC (method HPLC-A): *R*_t 6.61 min, chiral purity 100%.

Compound 5B:

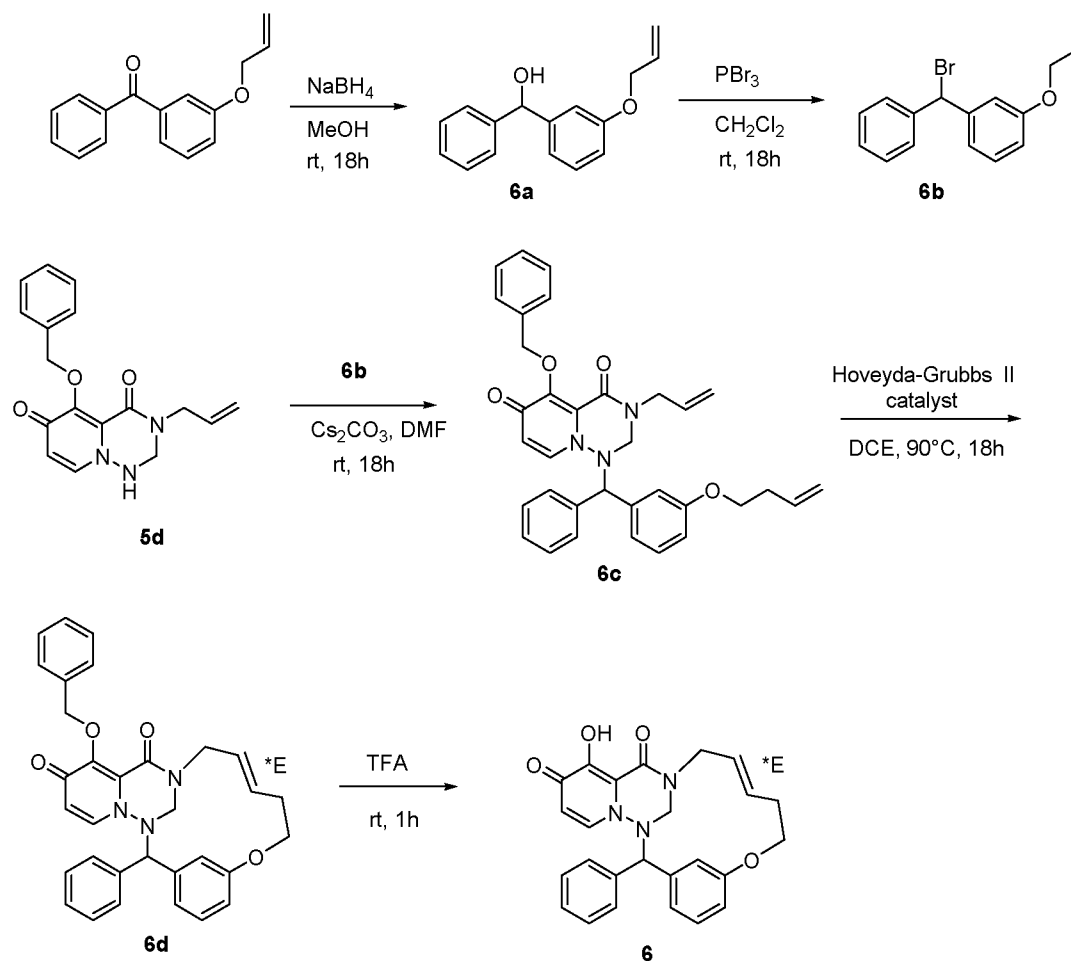
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.19 (br dd, *J*=13.6, 8.1 Hz, 1 H) 4.11 - 4.46 (m, 2 H) 4.54 - 4.89 (m, 2 H) 5.11 (br d, *J*=13.6 Hz, 1 H) 5.31 (s, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.82 - 5.93 (m, 1 H) 6.06 - 6.28 (m, 1 H) 7.02 - 7.28 (m, 7 H) 7.28 - 7.55 (m, 2 H) 8.09 (br d, *J*=7.6 Hz, 1 H)

LC/MS (method LC-B): *R*_t 2.25 min, MH⁺ 416

$[\alpha]_D^{20}$: +688.44° (c 0.32, DMF)

Chiral HPLC (method HPLC-A): *R*_t 5.55 min, chiral purity 100%.

Example 6: synthesis of (**E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,3)-benzenacyclononaphan-7-ene-14,16-dione (compound **6**)



Synthesis of intermediate **6a**:

NaBH₄ (1.47 g, 38.7 mmol) was added portionwise to a solution of (3-(allyloxy)phenyl)(phenyl)methanone [CAS 93021-98-8] (7.5 g, 29.73 mmol) in MeOH (120 mL) at 0°C. The mixture was stirred at rt for 18 h. 10% NH₄Cl aqueous solution was added and the solution was extracted with CH₂Cl₂ twice. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford (3-(allyloxy)phenyl)(phenyl)methanol (intermediate **6a**, 7.43 g).

Synthesis of intermediate **6b**:

At 0°C, under N₂, PBr₃ (261 μL, 2.75 mmol) was added dropwise to a solution of ((3-(allyloxy)phenyl)(phenyl)methanol (intermediate **6a**, 700 mg, 2.75 mmol) in dry CH₂Cl₂ (8.4 mL). The mixture was warmed to rt and stirred for 18 h. The reaction was quenched with ice and the aqueous phase was extracted with CH₂Cl₂. The organic layer was washed with water, dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure to give 1-(allyloxy)-3-(bromo(phenyl)methyl)benzene (intermediate **6b**, 820 mg).

Synthesis of intermediate 6c:

3-allyl-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **5d**, 470 mg, 1.51 mmol) was solubilized in DMF (10 mL) and Cs₂CO₃ (2.46 g, 7.55 mmol) was added at 0°C. The reaction mixture was stirred for 1 h at 0°C. 1-(allyloxy)-3-(bromo(phenyl)methyl)benzene (intermediate **6b**, 718 mg, 2.26 mmol) was added and the mixture was stirred at rt for 18 h. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water, then with brine. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 µm, 40 g, CH₂Cl₂/CH₃OH from 100/0 to 97/3). The pure fractions were collected and evaporated to dryness to give 3-allyl-5-(benzyloxy)-1-((3-(but-3-en-1-yloxy)phenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **6c**, 0.45 g).

Synthesis of intermediate 6d:

Prior to the reaction, the solvent was degassed by bubbling N₂ through. In a pressure vessel, Hoveyda-Grubbs 2nd generation catalyst (100.7 mg, 0.16 mmol) was added to a solution of 3-allyl-5-(benzyloxy)-1-((3-(but-3-en-1-yloxy)phenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **6c**, 440 mg, 0.80 mmol) in DCE (66 mL) and the reaction mixture was stirred at 90°C for 18 h. SiliaMetS[®] DMT (2.1 g, 1.28 mmol) was added and the mixture was stirred at rt for 48 h. The reaction mixture was filtered through celite[®] and the filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 µm, 12 g, CH₂Cl₂/CH₃OH from 99/1 to 96/4). The pure fractions were collected and evaporated to dryness to give (**E*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-1*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,3)-benzenacyclononaphan-7-ene-14,16-dione (intermediate **6d**, only one conformation for the double bond, E not fully validated, 37 mg).

Synthesis of Compound 6:

At rt, TFA (0.55 mL, 7.12 mmol) was added in one portion to (**E*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-1*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,3)-benzenacyclononaphan-7-ene-14,16-dione (intermediate **6d**, 37 mg, 0.071 mmol) and the resulting mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 µm, 4 g, CH₂Cl₂/CH₃OH 96/4). The pure fractions were collected and evaporated to dryness (12 mg). The compound was crystallized from CH₃OH. The precipitate was filtered off and dried under vacuum to give (*E**)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-1*H*-

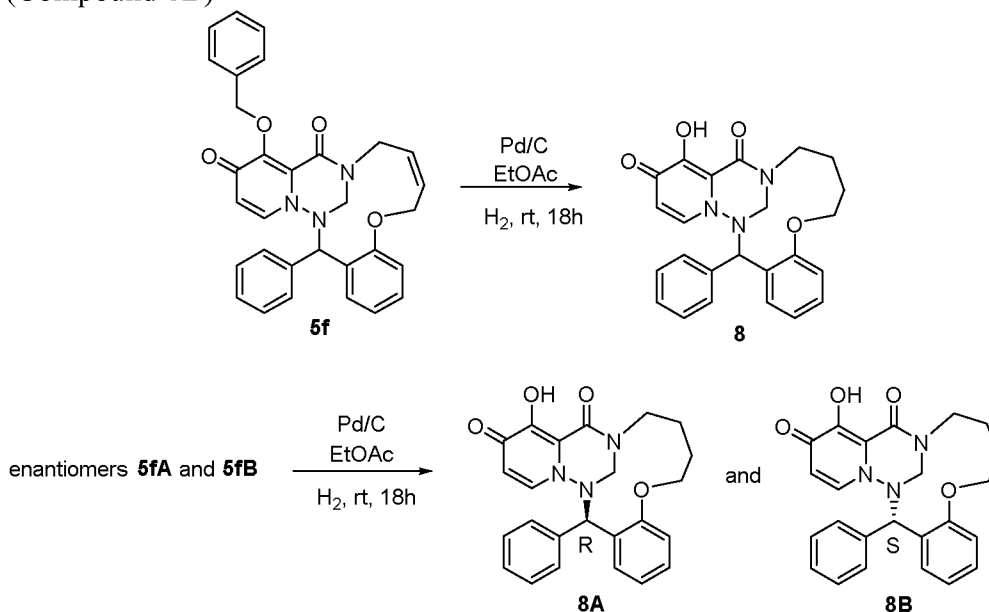
4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,3)-benzenacyclononaphan-7-ene-14,16-dione (Compound **6**, 3.7 mg).

Compound 6:

- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.00 (dd, *J*=14.0, 10.2 Hz, 1 H) 3.96 (d, *J*=13.2 Hz, 1 H) 4.07 (ddd, *J*=12.3, 6.0, 3.5 Hz, 1 H) 4.36 (br dd, *J*=13.9, 3.8 Hz, 1 H) 4.64 (ddd, *J*=11.9, 9.1, 2.4 Hz, 1 H) 4.96 (d, *J*=13.2 Hz, 1 H) 5.22 (s, 1 H) 5.37 - 5.48 (m, 1 H) 5.54 (d, *J*=7.9 Hz, 1 H) 5.77 (ddd, *J*=15.2, 10.5, 4.3 Hz, 1 H) 6.91 (dd, *J*=8.0, 1.4 Hz, 1 H) 7.22 (d, *J*=7.9 Hz, 1 H) 7.23 - 7.31 (m, 3 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.42 (m, 1 H) 7.60 (br s, 2 H) 11.32 - 12.02 (m, 1 H) (2 protons under DMSO peak)
- 10 LC/MS (method LC-A): R_t 2.57 min, MH⁺ 430

Example 8: synthesis of 12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

- 15 (Compound **8**) and its enantiomers (18*R*)-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **8A**) and (18*S*)-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **8B**)



Synthesis of Compound 8:

Under an atmospheric pressure of H₂, (Z)-12-(benzyloxy)-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

- 25 (intermediate **5f**, 67 mg, 0.13 mmol) and Pd/C (10%) (71 mg, 0.07 mmol) in EtOAc (3.9 mL) were stirred at rt for 18 h. The catalyst was removed by filtration through celite[®].

The celite[®] was washed with EtOAc, and then with CH₂Cl₂/MeOH. The filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (regular 30 µm, 4 g, CH₂Cl₂/CH₃OH from 99/1 to 97/3). The pure fractions were collected and concentrated under reduced pressure. The residue
5 was freeze-dried in CH₃CN/water to give 12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **8**, 21 mg).

Synthesis of Compound **8A**:

10 (18*R*)-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **8A**, 15 mg) was obtained using the procedure described for compound **8** starting from intermediate **5fA**.

Synthesis of Compound **8B**:

15 (18*S*)-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **8B**, 25 mg) was obtained using the procedure described for compound **8** starting from intermediate **5fB**.

Compound **8**:

¹H NMR (500 MHz, Chloroform-*d*) δ ppm 1.10 - 1.23 (m, 1 H) 1.56 - 1.73 (m, 1 H) 1.88 - 2.09 (m, 2 H) 2.55 (dt, *J*=14.2, 3.0 Hz, 1 H) 4.12 - 4.23 (m, 1 H) 4.30 - 4.41 (m, 2 H) 4.41 - 4.50 (m, 1 H) 4.87 (d, *J*=13.2 Hz, 1 H) 5.80 (br d, *J*=7.6 Hz, 1 H) 6.04 (s, 1 H)
25 6.82 (d, *J*=7.9 Hz, 1 H) 7.06 (d, *J*=8.2 Hz, 1 H) 7.18 - 7.25 (m, 4 H) 7.31 - 7.48 (m, 3 H) 7.88 - 7.96 (m, 1 H)

LC/MS (method LC-A): *R*_t 2.48 min, MH⁺ 418

Compound **8A**:

30 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.16 (m, 1 H) 1.50 - 1.66 (m, 1 H) 1.75 - 2.00 (m, 2 H) 2.67 (br s, 1 H) 4.04 (br t, *J*=12.9 Hz, 1 H) 4.13 - 4.29 (m, 2 H) 4.38 (br d, *J*=12.1 Hz, 1 H) 5.01 (d, *J*=13.1 Hz, 1 H) 5.51 (d, *J*=7.6 Hz, 1 H) 5.91 (s, 1 H) 7.13 - 7.28 (m, 6 H) 7.30 - 7.43 (m, 3 H) 7.98 (br d, *J*=7.1 Hz, 1 H) 11.43 (br s, 1 H)

LC/MS (method LC-A): *R*_t 2.47 min, MH⁺ 418

35 [α]_D²⁰: -319.13° (c 0.115, DMF)

Chiral HPLC (method HPLC-B): *R*_t 7.75 min, chiral purity 100%.

Compound 8B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.99 - 1.13 (m, 1 H) 1.52 - 1.65 (m, 1 H) 1.75 - 1.99 (m, 2 H) 2.64 (br s, 1 H) 4.04 (br t, *J*=12.9 Hz, 1 H) 4.18 (t, *J*=11.3 Hz, 1 H) 4.25 (d, *J*=13.6 Hz, 1 H) 4.38 (br d, *J*=12.3 Hz, 1 H) 5.01 (d, *J*=13.6 Hz, 1 H) 5.52 (d, *J*=7.6 Hz, 1 H) 5.91 (s, 1 H) 7.16 - 7.28 (m, 6 H) 7.31 - 7.42 (m, 3 H) 7.98 (d, *J*=6.6 Hz, 1 H) 10.60 - 12.15 (m, 1 H)

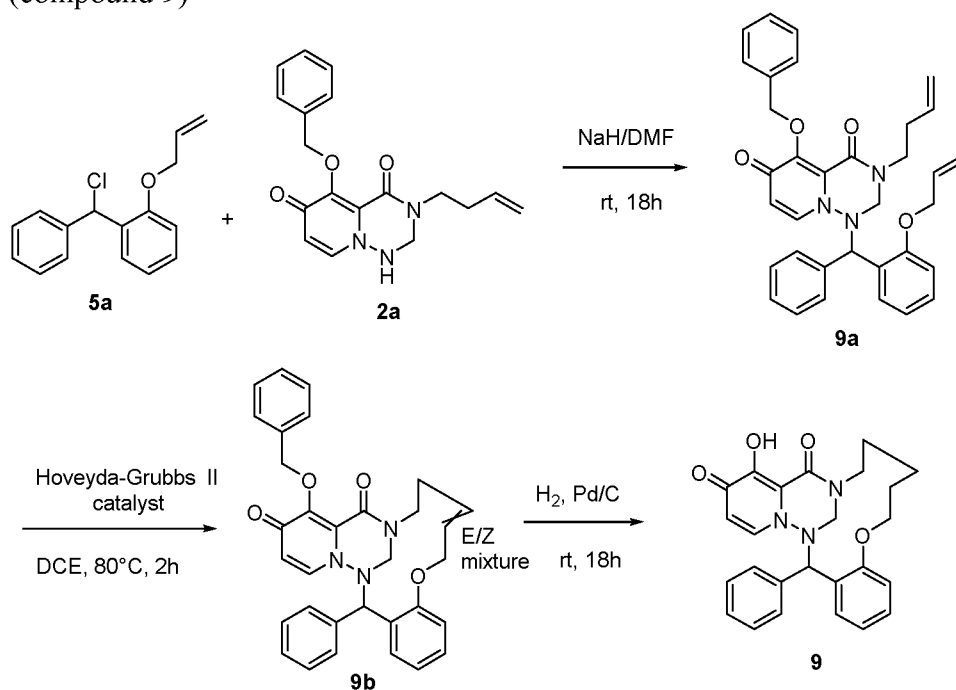
LC/MS (method LC-A): *R*_t 2.47 min, *MH*⁺ 418

[α]_D²⁰: +296.75° (c 0.123, DMF)

Chiral HPLC (method HPLC-B): *R*_t 5.07 min, chiral purity 100%.

10

Example 9: synthesis of 15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphane-14,16-dione (compound **9**)



15

Synthesis of intermediate 9a:

1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **9a**, 8.4 g) was obtained using the procedure described for intermediate **5e** starting from intermediate **2a**.

20

Synthesis of intermediate 9b:

15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (intermediate **9b**,

undefined *E/Z* mixture, 925 mg) was obtained using the procedure described for intermediate **5f**.

Synthesis of Compound 9:

15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-

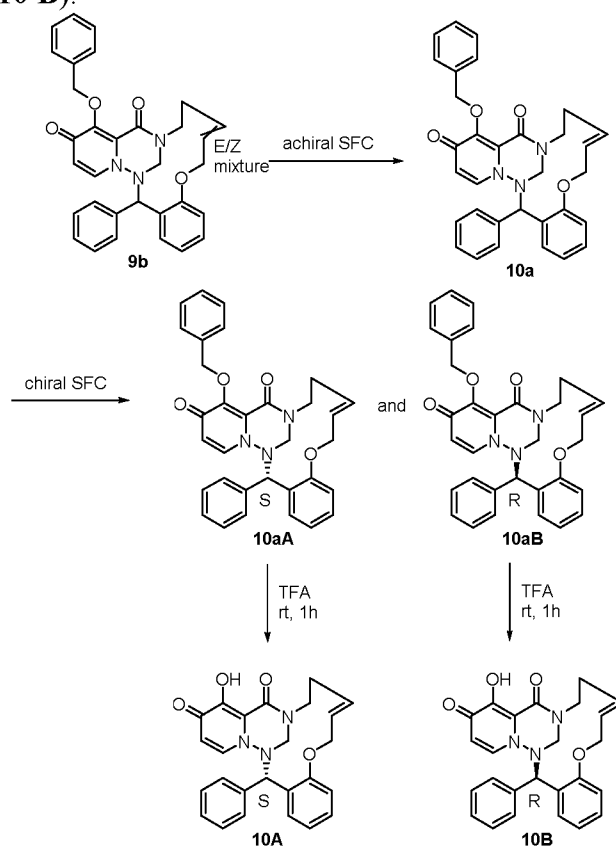
5 *f*][1,2,4]triazina-3(1,2)-benzenacyclononaphane-14,16-dione (compound **9**, 29 mg) was obtained using the procedure described for compound **8**.

Compound 9:

¹H NMR (500 MHz, Chloroform-*d*) δ ppm 0.98 - 1.13 (m, 1 H) 1.31 - 1.47 (m, 1 H) 1.47 - 1.62 (m, 1 H) 1.63 - 1.82 (m, 1 H) 1.98 2.08 (m, 1H) 2.11-2.25 (m, 1 H) 2.55 - 2.64 (m, 1 H) 3.88 (td, *J*=10.6, 4.3 Hz, 1 H) 4.24 (d, *J*=13.2 Hz, 1 H) 4.28 - 4.37 (m, 2 H) 4.80 (d, *J*=12.9 Hz, 1 H) 5.70 (br d, *J*=6.9 Hz, 1 H) 5.98 (s, 1 H) 6.73 (d, *J*=7.6 Hz, 1 H) 6.87 (d, *J*=8.2 Hz, 1 H) 7.07 - 7.12 (m, 6 H) 7.18 - 7.29 (m, 1 H) 7.89 (d, *J*=7.7 Hz, 1 H)

LC/MS (method LC-A): *R*_t 2.60 min, *MH*⁺ 432

15 Example 10: synthesis of (2*S,E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **10A**) and (2*R,E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **10B**).



Synthesis of intermediate 10a:

Intermediate **9b** (925 mg) was purified via achiral SFC (Stationary phase: NH₂ 5 µm 150 x 30 mm, mobile phase: 80% CO₂, 20% EtOH). The pure fractions were combined and concentrated under reduced pressure to give (*E*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (intermediate **10a**, 648 mg).

Synthesis of intermediates 10aA and 10aB:

The two enantiomers of intermediate **10a** (1.1 g) were separated via chiral SFC (Stationary phase: Whelk O1 (*S,S*) 5 µm 250 x 21.1 mm, Mobile phase: 55% CO₂, 45% MeOH). The pure fractions were collected and concentrated under reduced pressure to give the first eluted enantiomer (enantiomer **10aA**, 470 mg) and the second eluted enantiomer (enantiomer **10aB**, 487 mg).

Synthesis of Compound 10A:

(2*S,E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **10A**, 193 mg) was obtained using the procedure described for compound **5A**.

Compound 10A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.22 (br d, *J*=12.6 Hz, 1 H) 2.74 - 2.94 (m, 2 H) 3.70 - 3.83 (m, 1 H) 4.13 - 4.22 (m, 1 H) 4.28 (d, *J*=12.9 Hz, 1 H) 4.71 (dd, *J*=11.8, 5.2 Hz, 1 H) 5.06 (d, *J*=12.9 Hz, 1 H) 5.38 (d, *J*=7.6 Hz, 1 H) 5.44 - 5.55 (m, 1 H) 5.93 (s, 1 H) 5.99 (ddd, *J*=15.3, 10.1, 5.2 Hz, 1 H) 6.92 - 7.27 (m, 7 H) 7.28 - 7.35 (m, 1 H) 7.37 - 7.44 (m, 1 H) 8.01 (dd, *J*=7.6, 1.3 Hz, 1 H) 11.74 (br s, 1 H)

LC/MS (method LC-B): R_t 2.38 min, MH⁺ 430

[α]_D²⁰: +409.12° (c 0.274, DMF)

MP = 212°C

Synthesis of Compound 10B:

(2*R,E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **10 B**, 213 mg) was obtained using the procedure described for compound **5A**.

Compound 10B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.22 (br d, *J*=13.2 Hz, 1 H) 2.86 (quin, *J*=12.4 Hz, 2 H) 3.72 - 3.86 (m, 1 H) 4.18 (t, *J*=11.0 Hz, 1 H) 4.28 (d, *J*=13.2 Hz, 1 H) 4.71 (dd,

$J=11.8, 5.2$ Hz, 1 H) 5.06 (d, $J=12.9$ Hz, 1 H) 5.38 (d, $J=7.6$ Hz, 1 H) 5.50 (td, $J=10.0, 4.9$ Hz, 1 H) 5.93 (s, 1 H) 5.99 (ddd, $J=15.1, 9.8, 5.0$ Hz, 1 H) 6.88 - 7.26 (m, 7 H) 7.29 - 7.35 (m, 1 H) 7.37 - 7.45 (m, 1 H) 8.01 (d, $J=6.6$ Hz, 1 H) 11.57 - 11.88 (m, 1 H)

LC/MS (method LC-B): R_t 2.37 min, MH^+ 430

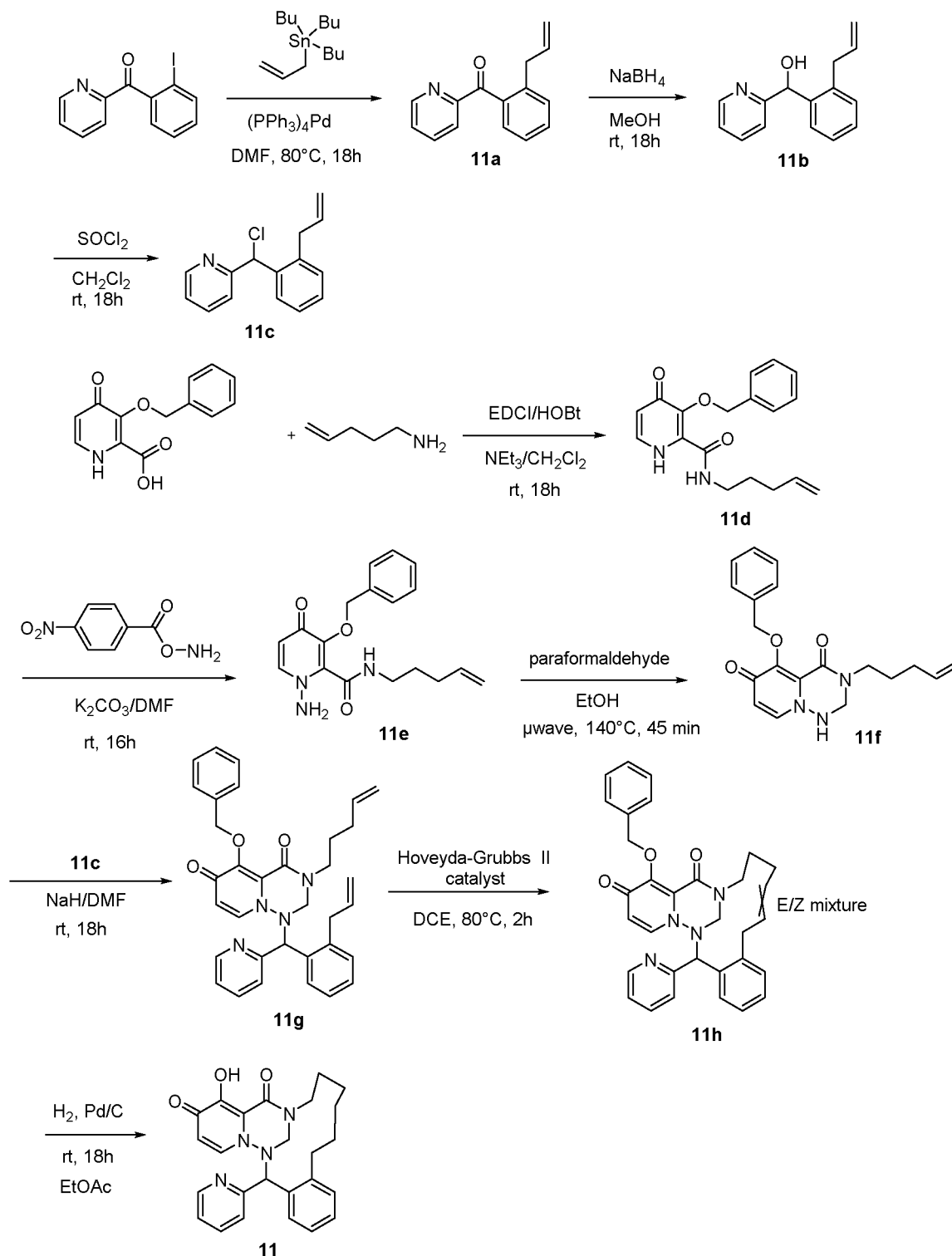
5 $[\alpha]_D^{20}$: -433.59° (c 0.259, DMF)

MP = 212°C

Example 11: synthesis of 15-hydroxy-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphane-14,16-dione

10 (Compound **11**).

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Synthesis of intermediate 11a:

To a solution of (2-iodophenyl)(pyridin-2-yl)methanone [CAS 76160-35-5] (1.5 g, 4.9 mmol) and allyltri-*N*-butyltin (1.8 mL, 5.8 mmol) in DMF (38 mL, degassed under nitrogen) was added $(\text{PPh}_3)_4\text{Pd}$ (0.28 g, 0.24 mmol). The mixture was stirred at 80°C for 18 h. The mixture was partitioned between EtOAc and brine. The organic layer was

washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μm , 40 g, heptane/EtOAc from 90/10 to 80/20). The pure fractions were combined and concentrated under reduced pressure to give (2-allylphenyl)(pyridin-2-yl)methanone (intermediate **11a**, 0.68 g).

Synthesis of intermediate 11b:

NaBH_4 (0.23 g, 6.1 mmol) was added portionwise to a solution of (2-allylphenyl)(pyridin-2-yl)methanone (intermediate **11a**, 0.68 g, 3.0 mmol) in MeOH (12 mL) at 0°C . The mixture was then stirred at 0°C for 1.5 h then at rt for 18 h. 10% NH_4Cl aqueous solution was added and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure to afford (2-allylphenyl)(pyridin-2-yl)methanol (intermediate **11b**, 0.63 g), which was used as such in the next step.

Synthesis of intermediate 11c:

SOCl_2 (0.24 mL, 3.4 mmol) was added dropwise to a solution of (2-allylphenyl)(pyridin-2-yl)methanol (intermediate **11b**, 0.63 g, 2.8 mmol) in CH_2Cl_2 (6.9 mL) at 5°C . The mixture was stirred at 5°C for 1 h and at rt for 18 h. The solvent was evaporated to dryness and the residue co-evaporated with toluene to yield 2-((2-allylphenyl)chloromethyl)pyridine (intermediate **11c**, 0.90 g), which was used as such in the next step.

Synthesis of intermediate 11d:

3-(benzyloxy)-4-oxo-*N*-(pent-4-en-1-yl)-1,4-dihydropyridine-2-carboxamide (intermediate **11d**, 4.7 g) was obtained using the procedure described for intermediate **1a** starting from pent-4-enylamine [CAS 22537-07-1].

Synthesis of intermediate 11e:

1-amino-3-(benzyloxy)-4-oxo-*N*-(pent-4-en-1-yl)-1,4-dihydropyridine-2-carboxamide (intermediate **11e**, 3.9 g) was obtained using the procedure described for intermediate **1b**.

Synthesis of intermediate 11f:

5-(benzyloxy)-3-(pent-4-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **11f**, 5 g), used as such in the next step, was obtained using the procedure described for compound **5d**.

Synthesis of intermediate 11g:

1-((2-allylphenyl)(pyridin-2-yl)methyl)-5-(benzyloxy)-3-(pent-4-en-1-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **11g**, 350 mg) was obtained using the procedure described for intermediate **5e**.

5

Synthesis of intermediate 11h:

15-(benzyloxy)-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11H-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-5-ene-14,16-dione (intermediate **11h**, undetermined mixture of *E/Z* isomers, 200 mg), used as such in the next step, was obtained using the procedure described for intermediate **5f**.

10

Synthesis of Compound 11:

15-hydroxy-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11H-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphane-14,16-dione (Compound **11**, 40 mg) was obtained using the procedure described for compound **8**.

15

Compound 11:

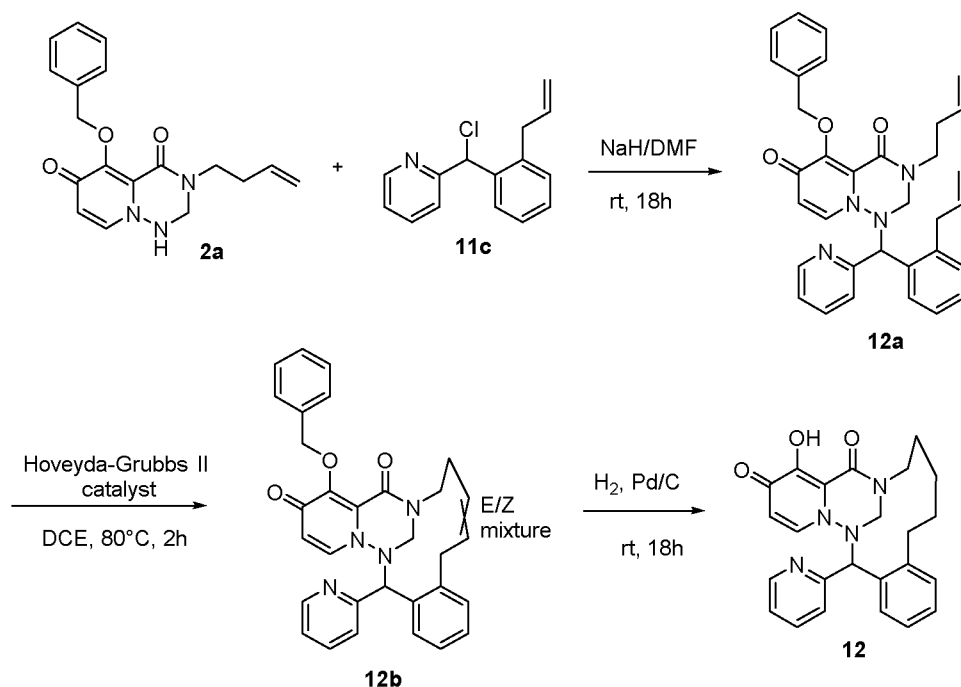
¹H NMR (500 MHz, Chloroform-*d*) δ ppm 0.68 - 0.87 (m, 1 H) 0.89 - 1.10 (m, 1 H) 1.25 - 1.47 (m, 2 H) 1.72 - 1.90 (m, 3 H) 2.27 - 2.38 (m, 1 H) 2.40 - 2.57 (m, 1 H) 2.60 - 2.71 (m, 2 H) 3.93 (dt, *J*=13.5, 4.5 Hz, 1 H) 4.36 (d, *J*=12.9 Hz, 1 H) 4.96 (d, *J*=12.9 Hz, 1 H) 5.69 (br d, *J*=7.6 Hz, 1 H) 6.15 (s, 1 H) 6.74 (d, *J*=7.6 Hz, 1 H) 6.98 - 7.16 (m, 2 H) 7.29 (t, *J*=7.4 Hz, 1 H) 7.34 (t, *J*=7.6 Hz, 1 H) 7.42 (td, *J*=7.7, 1.9 Hz, 1 H) 8.03 (d, *J*=7.7 Hz, 1 H) 8.32 (d, *J*=4.1 Hz, 1 H)

20

LC/MS (method LC-A): *R*_t 2.63 min, *MH*⁺ 431

25

Example 12: synthesis of 4-hydroxy-16-(pyridin-2-yl)-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[k]pyrido[1,2-b][1,2,5]triazacyclotridecine-3,5-dione (Compound **12**).



Synthesis of Compound 12:

Compound 12 (8 mg) was obtained using the procedures described in example 11.

5

Compound 12:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.67 - 0.88 (m, 1 H) 1.29 - 1.41 (m, 1 H) 1.42 - 1.60 (m, 2 H) 1.70 - 1.81 (m, 1 H) 1.92 - 2.06 (m, 1 H) 2.52 - 2.59 (m, 1 H) 2.62 - 2.67 (m, 1 H) 2.79 - 2.88 (m, 1 H) 3.99 (br t, *J*=12.8 Hz, 1 H) 4.37 (d, *J*=13.6 Hz, 1 H) 5.08 (br d, *J*=13.9 Hz, 1 H) 5.52 (d, *J*=7.6 Hz, 1 H) 5.82 (s, 1 H) 7.05 (d, *J*=7.9 Hz, 1 H) 7.20 - 7.30 (m, 2 H) 7.33 (t, *J*=6.9 Hz, 1 H) 7.41 (t, *J*=7.6 Hz, 1 H) 7.63 (d, *J*=7.9 Hz, 1 H) 7.71 (td, *J*=7.7, 1.6 Hz, 1 H) 8.06 (d, *J*=7.6 Hz, 1 H) 8.42 (d, *J*=4.1 Hz, 1 H) 11.35 (br s, 1 H)

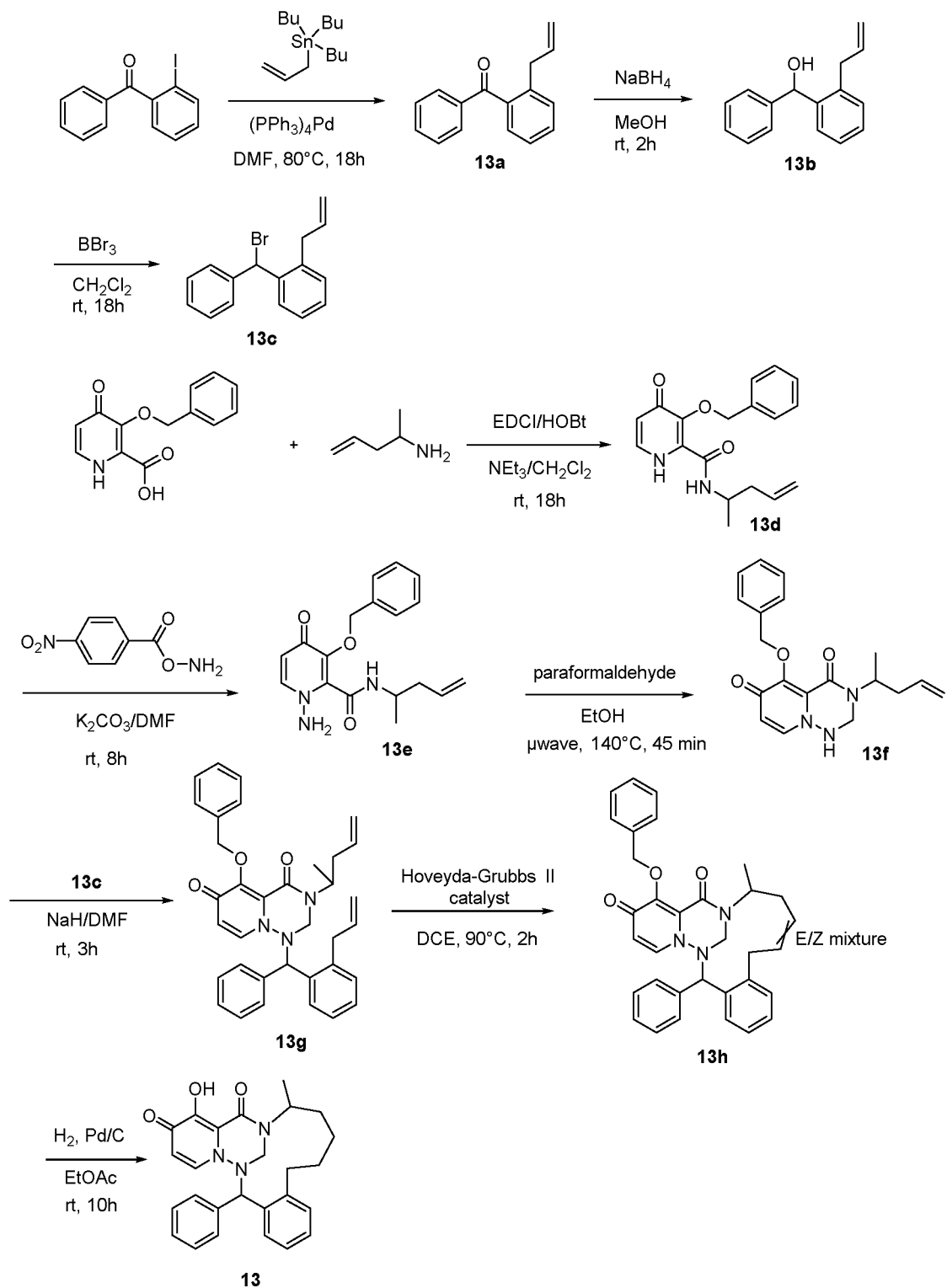
LC/MS (method LC-A): R_t 2.35 min, MH⁺ 415

15

Example 13: synthesis of 4-hydroxy-7-methyl-15-phenyl-8,9,10,15-tetrahydro-7H-6,16-methanobenzo[*j*]pyrido[1,2-*b*][1,2,5]triazacyclododecine-3,5-dione (Compound 13).

20

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**Synthesis of intermediate 13b:**

2-allylphenyl)(phenyl)methanol (intermediate **13b**, 4.5 g) was obtained using the
 5 procedures described in example 11.

Synthesis of intermediate 13c:

1-allyl-2-(bromo(phenyl)methyl)benzene (intermediate **13c**, 1.28 g) was obtained using the procedure described for intermediate **6b**.

Synthesis of intermediate 13f:

- 5 5-(benzyloxy)-3-(pent-4-en-2-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **13f**, 1.12 g) was obtained using the procedures described for intermediate **2a**.

Synthesis of intermediate 13g:

- 10 1-((2-allylphenyl)(phenyl)methyl)-5-(benzyloxy)-3-(pent-4-en-2-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **13g**, 410 mg) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 13h:

- 15 4-(benzyloxy)-7-methyl-16-phenyl-7,8,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (undefined *E/Z* mixture, intermediate **13e**, 140 mg) was obtained using the procedure described for intermediate **5f**.

Synthesis of Compound 13:

- 20 4-hydroxy-7-methyl-15-phenyl-8,9,10,15-tetrahydro-7*H*-6,16-methanobenzo[*j*]pyrido[1,2-*b*][1,2,5]triazacyclododecine-3,5-dione (compound **13**, 29 mg) was obtained using the procedure described for compound **8**.

Compound 13:

major diastereoisomer (55%)

¹H NMR (500 MHz, Chloroform-*d*) δ ppm 0.91 (d, *J*=6.9 Hz, 3H) 1.17 - 1.73 (m, 4H) 1.87 - 2.14 (m, 3H) 2.46 - 2.75 (m, 2H) 4.45 (d, *J*=13.2 Hz, 1H) 4.56 - 4.71 (m, 2H) 5.60 (s, 1 H) 5.63 (dd, *J*=7.6, 5.7 Hz, 1H) 6.54 (d, *J*=7.9 Hz, 1H) 7.08 - 7.18 (m, 5H) 7.20 - 7.37 (m, 3H) 7.87 (d, *J*=7.6 Hz, 1H)

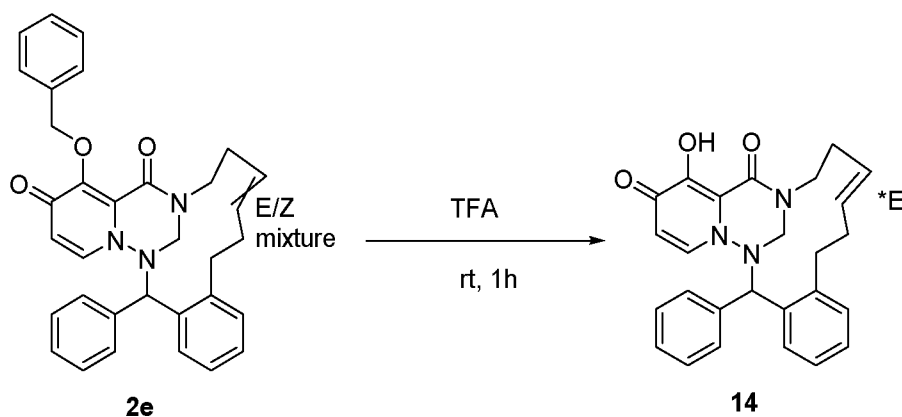
minor diastereoisomer (45%)

¹H NMR (500 MHz, Chloroform-*d*) δ ppm 1.17 - 1.73 (m, 7H) 1.87 - 2.14 (m, 3H) 2.46 - 2.75 (m, 1H) 2.72 - 2.80 (m, 1H) 2.81 - 2.93 (m, 1H) 4.28 (d, *J*=13.2 Hz, 1H) 4.91 (d, *J*=12.9 Hz, 1H) 5.63 (dd, *J*=7.6, 5.7 Hz, 1H) 5.71 (s, 1H) 6.63 (d, *J*=7.6 Hz, 1H) 7.08 - 7.18 (m, 5H) 7.20 - 7.37 (m, 3H) 7.89 (d, *J*=7.9 Hz, 1H)

LC/MS (method LC-A): *R*_t 2.93 min, MH⁺ 430

MP > 260°C

Example 14: synthesis of (*E)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **14**).



5

Synthesis of Compound **14**:

(*E)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **14**, 25 mg) was obtained using the procedure described for compound **5A**.

10

Compound **14**:

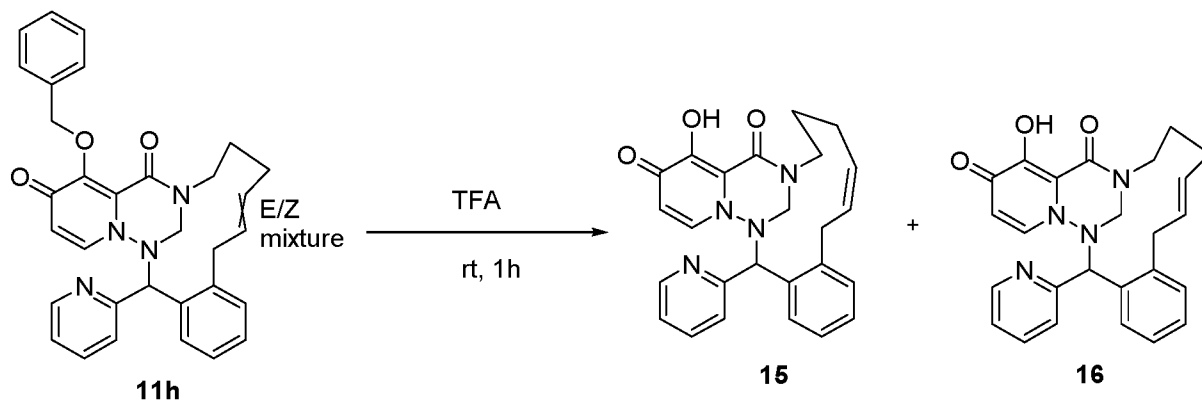
¹H NMR (500 MHz, Chloroform-*d*) δ ppm 1.96 - 2.07 (m, 1 H) 2.15 (br d, *J*=14.2 Hz, 1 H) 2.27 - 2.39 (m, 2 H) 2.44 - 2.59 (m, 2 H) 2.82 - 2.95 (m, 1 H) 3.96 (dt, *J*=13.7, 3.9 Hz, 1 H) 4.39 (d, *J*=12.6 Hz, 1 H) 4.88 (d, *J*=12.6 Hz, 1 H) 5.02 (ddd, *J*=15.0, 10.2, 4.4 Hz, 1 H) 5.53 (d, *J*=7.6 Hz, 1 H) 5.69 (ddd, *J*=14.9, 10.0, 5.0 Hz, 1 H) 5.85 (s, 1 H) 6.51 (d, *J*=7.9 Hz, 1 H) 6.81 (br d, *J*=6.9 Hz, 1 H) 6.98 (br s, 1 H) 7.03 - 7.08 (m, 1 H) 7.09 - 7.15 (m, 3 H) 7.24 - 7.37 (m, 2 H) 7.86 (d, *J*=7.6 Hz, 1 H)

LC/MS (method LC-B): *R*_t 2.69 min, *MH*⁺ 428

20

Examples 15 and 16: synthesis of (Z)-15-hydroxy-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11H-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-5-ene-14,16-dione (Compound **15**) and (E)-15-hydroxy-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11H-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-5-ene-14,16-dione (Compound **16**).

25



Synthesis of Compounds 15 and 16:

(*Z*)-15-hydroxy-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-5-ene-14,16-dione (Compound **15**, 5 mg) and (*E*)-15-hydroxy-2-(pyridin-2-yl)-12,13,14,16-tetrahydro-11*H*-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-5-ene-14,16-dione (Compound **16**, 12 mg) were obtained using the procedure described for compound **5A**. The two isomers were separated via Reverse phase (Stationary phase: YMC-actus Triart-C18 10 μm 30x150 mm, Mobile phase: gradient from 75% formic acid 0.1%, 25% CH_3CN to 35% formic acid 0.1%, 65% CH_3CN).

Compound 15:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 0.59 - 0.73 (m, 1 H) 1.52 - 1.63 (m, 1 H) 1.81 - 1.94 (m, 1 H) 2.35 - 2.54 (m, 2 H) 2.64 - 2.72 (m, 1 H) 3.62 - 3.70 (m, 1 H) 3.92 - 4.06 (m, 1 H) 4.22 - 4.30 (m, 1 H) 4.93 - 5.07 (m, 1 H) 5.36 - 5.46 (m, 1 H) 5.55 - 5.65 (m, 1 H) 5.83 - 5.95 (m, 1 H) 6.01 (s, 1 H) 7.02 - 7.26 (m, 4 H) 7.28-7.36 (m, 1 H) 7.42 (d, $J=7.9$ Hz, 1 H) 7.59 (dt, $J=1.3, 7.6$ Hz, 1 H) 8.04 (d, $J=7.9$ Hz, 1 H) 8.32 (d, $J=3.8$ Hz, 1 H)

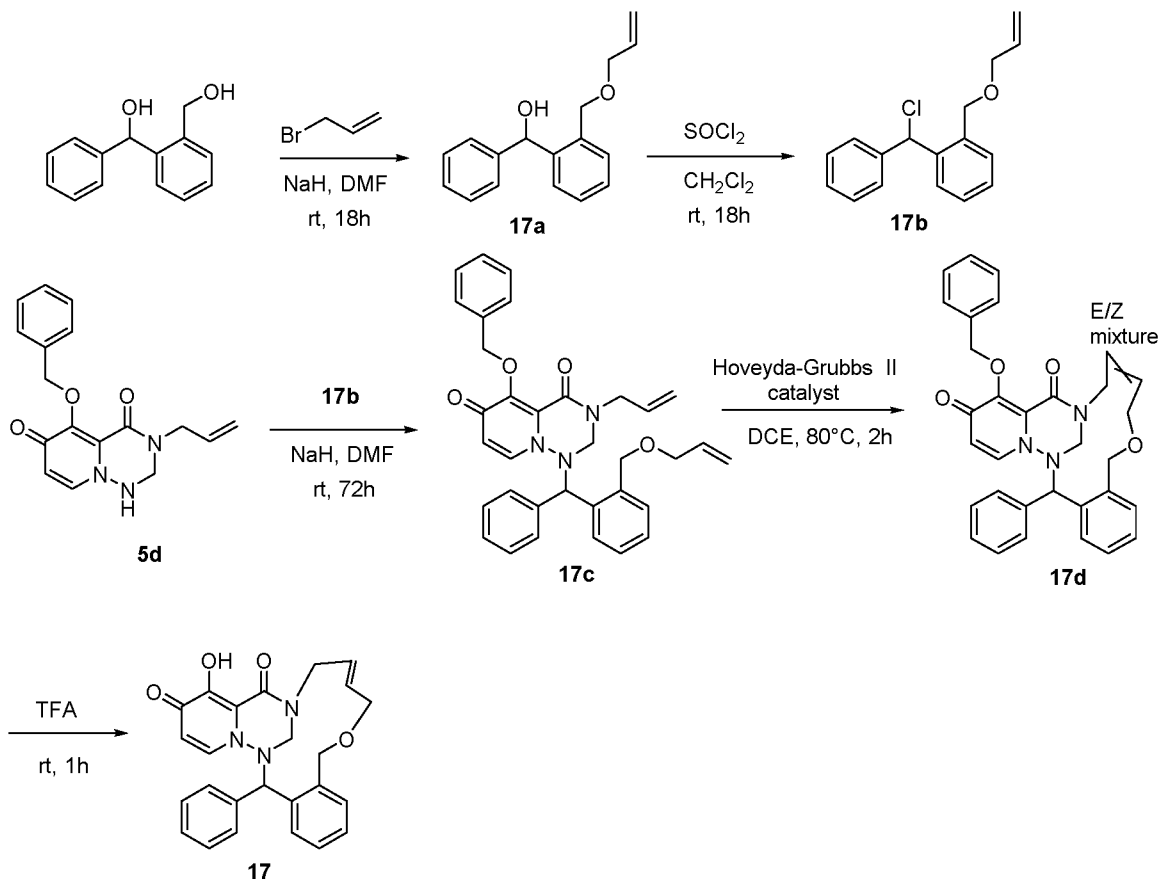
LC/MS (method LC-A): R_t 2.35 min, MH^+ 429

Compound 16:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.76 - 1.88 (m, 1 H) 1.93 - 2.04 (m, 1 H) 2.12 - 2.21 (m, 1 H) 2.21 - 2.31 (m, 1 H) 2.74 - 2.83 (m, 1 H) 3.05 - 3.2 (m, 2 H) 3.80 - 3.92 (m, 1 H) 4.24 (d, $J=12.6$ Hz, 1 H) 5.00 (d, $J=12.6$ Hz, 1 H) 5.42 (d, $J=7.6$ Hz, 1 H) 5.43 - 5.54 (m, 1 H) 5.65 - 5.72 (m, 1 H) 5.98 (s, 1 H) 7.15 (d, $J=6.6$ Hz, 1 H) 7.20 (dd, $J=7.1, 5.2$ Hz, 1 H) 7.28 - 7.36 (m, 3 H) 7.48 (t, $J=7.3$ Hz, 1 H) 7.62 (td, $J=7.7, 1.9$ Hz, 1 H) 8.29 (d, $J=7.7$ Hz, 1 H) 8.33 (d, $J=5.0$ Hz, 1 H) 11.78 (br s, 1 H)

LC/MS (method LC-A): R_t 2.40 min, MH^+ 429

Example 17: synthesis of (*E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-5-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-7-ene-14,16-dione (Compound 17).



Synthesis of intermediate 17a:

A mixture of allyl bromide (0.11 mL, 1.3 mmol), (2-(hydroxymethyl)phenyl)(phenyl)methanol [CAS 1586-01-2] (0.25 g, 1.2 mmol) and NaH (60% dispersion in mineral oil) (51 mg, 1.3 mmol) in DMF (4.5 mL) was stirred at rt for 18 h. EtOAc was added and the mixture was washed 5 times with brine. The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μm , 12 g, heptane/EtOAc from 90/10 to 80/20). The pure fractions were collected and concentrated under vacuum to give (2-((allyloxy)methyl)phenyl)(phenyl)methanol (intermediate 17a, 90 mg).

Synthesis of intermediate 17b:

SOCl_2 (31 μL , 0.043 mmol) was added dropwise to a solution of (2-((allyloxy)methyl)phenyl)(phenyl)methanol (intermediate 17a, 90 mg, 0.35 mmol) in CH_2Cl_2 (0.88 mL) at 5°C. The mixture was stirred at 5°C for 1 h and at rt for 18 h. The

solvent was evaporated to dryness and the residue co-evaporated with toluene to give 1-((allyloxy)methyl)-2-(chloro(phenyl)methyl)benzene (intermediate **17b**, 90 mg), which was used as such in the next step.

5 **Synthesis of Compound 17:**

(*E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-5-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-7-ene-14,16-dione (Compound **17**, 27 mg) was obtained using the procedures described in example 5.

10 **Compound 17:**

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm (93% *E*, 7% *Z*) (spectrum of the major isomer)
3.23 - 3.29 (m, 1 H) 3.99 - 4.09 (m, 2 H) 4.16 - 4.22 (m, 1 H) 4.29 (d, *J*=13.6 Hz, 1 H)
4.46 (d, *J*=13.9 Hz, 1 H) 4.51 - 4.62 (m, 1 H) 5.16 - 5.24 (m, 1 H) 5.42 - 5.50 (m, 2 H)
5.55 - 5.69 (m, 1 H) 6.10 - 6.20 (m, 1 H) 7.16 - 7.29 (m, 6 H) 7.38 - 7.46 (m, 2 H) 7.46 -

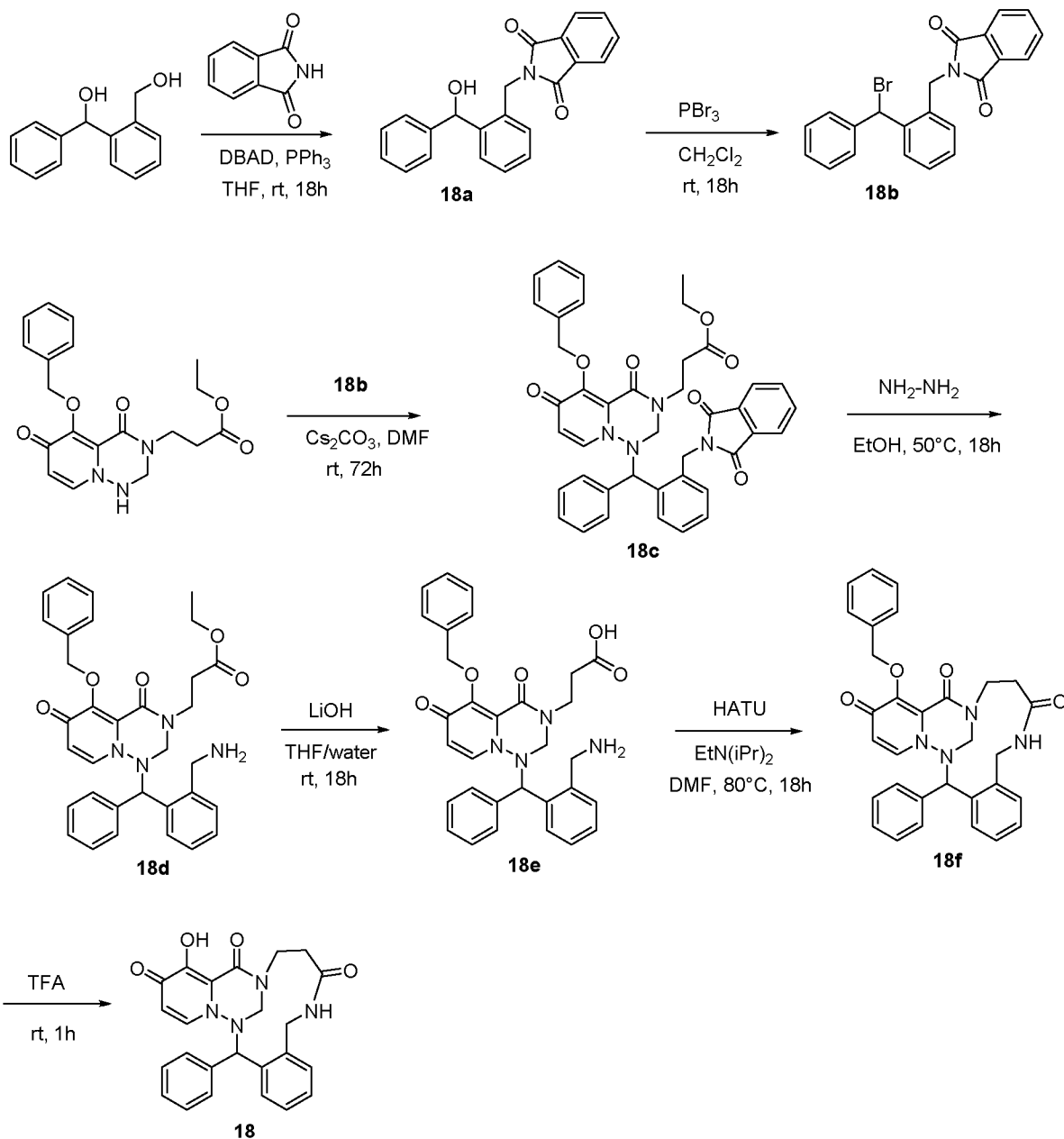
15 7.53 (m, 1 H) 8.08 - 8.18 (m, 1 H)

LC/MS (method LC-B): R_t 2.29 min, MH⁺ 430

Example 18: synthesis of 12-hydroxy-18-phenyl-5,8,9,18-tetrahydro-10,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5,9]tetraazacyclotridecine-7,11,13(6*H*)-trione (Compound **18**).

20

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**Synthesis of intermediate 18a:**

Under N_2 , a solution of (2-(hydroxymethyl)phenyl)(phenyl)methanol [CAS 1586-01-2] (1.5 g, 7.0 mmol), phthalimide (1.1 g, 7.7 mmol), di-*tert*-butyl azodicarboxylate (DBAD) (2.4 g, 11 mmol) and PPh_3 (2.8 g, 11 mmol) in dry THF (57 mL) was stirred for 18 h at rt. Celite[®] was added and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μm , 40 g, dry loading (celite[®]), heptane/EtOAc from 90/10 to 70/30). The pure fractions were collected and concentrated under reduced pressure to give 2-(2-(hydroxy(phenyl)methyl)benzyl)isoindoline-1,3-dione (intermediate **18a**, 730 mg).

Synthesis of intermediate 18b:

At 0°C, PBr₃ (0.20 mL, 2.1 mmol) was added dropwise to a solution of 2-(2-(hydroxy(phenyl)methyl)benzyl)isoindoline-1,3-dione (intermediate **18a**, 0.72 g, 2.1 mmol) in CH₂Cl₂ (6.7 mL). The mixture was warmed up to rt and stirred for 18 h. The reaction was quenched by the addition of ice and the aqueous phase was extracted with CH₂Cl₂. The organic layer was washed with water, dried over MgSO₄, filtered and the solvent was evaporated to dryness to give 2-(2-(bromo(phenyl)methyl)benzyl)isoindoline-1,3-dione (intermediate **18b**, 870 mg).

Synthesis of intermediate 18c:

Ethyl 3-(5-(benzyloxy)-1-((2-((1,3-dioxoisindolin-2-yl)methyl)phenyl)(phenyl)methyl)-4,6-dioxo-1,2,4,6-tetrahydro-3H-pyrido[2,1-f][1,2,4]triazin-3-yl)propanoate (intermediate **18c**, 360 mg) was obtained using the procedure described for intermediate **1d**.

Synthesis of intermediate 18d:

A mixture of ethyl 3-(5-(benzyloxy)-1-((2-((1,3-dioxoisindolin-2-yl)methyl)phenyl)(phenyl)methyl)-4,6-dioxo-1,2,4,6-tetrahydro-3H-pyrido[2,1-f][1,2,4]triazin-3-yl)propanoate (intermediate **18c**, 0.43 g, 0.62 mmol) and hydrazine monohydrate (0.57 mL, 9.3 mmol) in EtOH (8.9 mL) was heated at 50°C for 18 h. The mixture was cooled down to rt and concentrated to dryness with celite[®]. The residue was purified by flash chromatography over silica gel (30 µm, 12 g, dry loading (celite[®]), CH₂Cl₂/CH₃OH from 100/0 to 95/5). The pure fractions were collected and concentrated under reduced pressure to give ethyl 3-(1-((2-(aminomethyl)phenyl)(phenyl)methyl)-5-(benzyloxy)-4,6-dioxo-1,2,4,6-tetrahydro-3H-pyrido[2,1-f][1,2,4]triazin-3-yl)propanoate (intermediate **18d**, 80 mg).

Synthesis of intermediate 18e:

LiOH (17 mg, 0.71 mmol) was added to a mixture of ethyl 3-(1-((2-(aminomethyl)phenyl)(phenyl)methyl)-5-(benzyloxy)-4,6-dioxo-1,2,4,6-tetrahydro-3H-pyrido[2,1-f][1,2,4]triazin-3-yl)propanoate (intermediate **18d**, 80 mg, 0.14 mmol) in water (0.26) and THF (1.1 mL). The reaction mixture was stirred at rt for 18 h. The solution was concentrated under vacuum and co-evaporated with toluene. Purification was performed by flash chromatography over silica gel (30 µm, 4 g, from CH₂Cl₂/CH₃OH 96/4 to 88/12). The pure fractions were collected and concentrated under reduced pressure to give 3-(1-((2-(aminomethyl)phenyl)(phenyl)methyl)-5-(benzyloxy)-4,6-dioxo-1,2,4,6-tetrahydro-3H-pyrido[2,1-f][1,2,4]triazin-3-yl)propanoic acid (intermediate **18e**, 70 mg).

Synthesis of intermediate 18f:

A mixture of 3-(1-((2-(aminomethyl)phenyl)(phenyl)methyl)-5-(benzyloxy)-4,6-dioxo-1,2,4,6-tetrahydro-3H-pyrido[2,1-f][1,2,4]triazin-3-yl)propanoic acid (intermediate **18e**, 70 mg, 0.13 mmol), HATU (74 mg, 0.20 mmol) and *N,N*-diisopropylethylamine (86 μ L, 0.52 mmol) in DMF (10 mL) was stirred at 80°C for 18 h. EtOAc was added and the mixture was washed 5 times with brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 μ m, 4 g, CH₂Cl₂/CH₃OH from 100/0 to 97/3). The pure fractions were collected and evaporated to dryness to give 12-(benzyloxy)-18-phenyl-5,8,9,18-tetrahydro-10,17-methanobenzo[k]pyrido[1,2-b][1,2,5,9]tetraazacyclotridecine-7,11,13(6*H*)-trione (intermediate **18f**, 35 mg).

Synthesis of Compound 18:

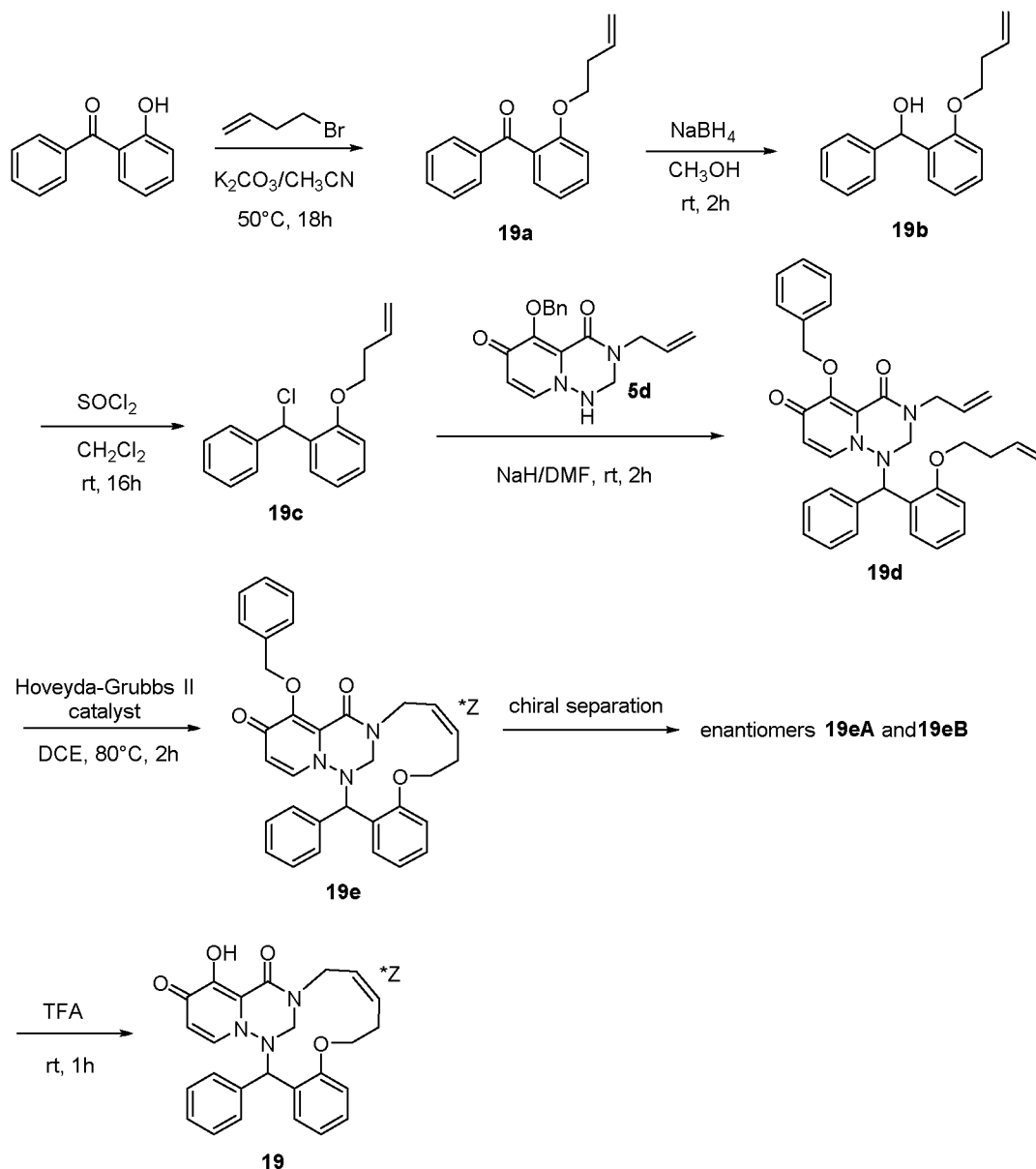
12-hydroxy-18-phenyl-5,8,9,18-tetrahydro-10,17-methanobenzo[k]pyrido[1,2-b][1,2,5,9]tetraazacyclotridecine-7,11,13(6*H*)-trione (Compound **18**, 22 mg) was obtained using the procedure described for compound **5A**.

Compound 18:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.26 - 2.32 (m, 1 H) 2.75 - 2.97 (m, 1 H) 2.97 - 3.14 (m, 1 H) 3.72 - 3.85 (m, 2 H) 3.95 (br d, *J*=12.6 Hz, 1 H) 4.42 (br s, 1 H) 5.02 (br d, *J*=12.6 Hz, 1 H) 5.38 (br d, *J*=7.6 Hz, 1 H) 5.88 (br s, 1 H) 7.10 - 7.59 (m, 9 H) 8.22 (br d, *J*=7.6 Hz, 1 H) 8.75 (br s, 1 H) 11.53 (br s, 1 H)
LC/MS (method LC-A): R_t 1.98 min, MH⁺ 431

Example 19: synthesis of (**Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-7-ene-14,16-dione (compound **19**)

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Synthesis of intermediate **19a**:

A mixture of 4-bromo-1-butene [CAS 5162-44-7] (10.2 mL, 101 mol), (2-hydroxyphenyl)(phenyl)methanone [CAS 117-99-7] (5 g, 25.224 mol) and K_2CO_3 (10.46 g, 75.673 mol) in CH_3CN (66 mL) was stirred at $50^\circ C$ for 18 h. The reaction was not complete and 4-bromo-1-butene (7.0 mL, 70 mmol) was added again. The mixture was stirred for another 24 h at $50^\circ C$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (20-45 μm , 120 g, heptane/EtOAc 90/10). The pure fractions were collected and concentrated to dryness under reduced pressure to give (2-(but-3-en-1-yloxy)phenyl)(phenyl)methanone (intermediate **19a**, 2 g).

Synthesis of intermediate 19b:

(2-(but-3-en-1-yloxy)phenyl)(phenyl)methanol (intermediate **19b**, 2.1 g) was obtained using the procedure described for intermediate **11b**.

5 Synthesis of intermediate 19c:

1-(but-3-en-1-yloxy)-2-(chloro(phenyl)methyl)benzene (intermediate **19c**, 2.2 g) was obtained with the procedure described for intermediate **5a**.

Synthesis of intermediate 19d:

- 10 3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yloxy)phenyl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **19d**, 2.45 g) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 19e:

- 15 (*Z)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-7-ene-14,16-dione (intermediate **19e**, 1.35 g) was obtained using the procedure described for intermediate **5f**. The two enantiomers were separated via chiral SFC (Stationary phase: Whelk O1 (*S,S*) 5 μ m 250 x 21.1 mm, Mobile phase: 60% CO₂, 40% MeOH) to give the first eluted enantiomer
20 **19eA** (531 mg) and the second eluted enantiomer **19eB** (536 mg).

Synthesis of Compound 19:

- (*Z)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-7-ene-14,16-dione (compound **19**, 101
25 mg, racemate (full racemization occurred during this step) was obtained using the procedure described for compound **5A**.

Enantiomer **19eB** (270 mg, 0.52 mmol) was treated under the same conditions and gave the same compound **19** (110 mg, racemate (full racemization occurred during this step).

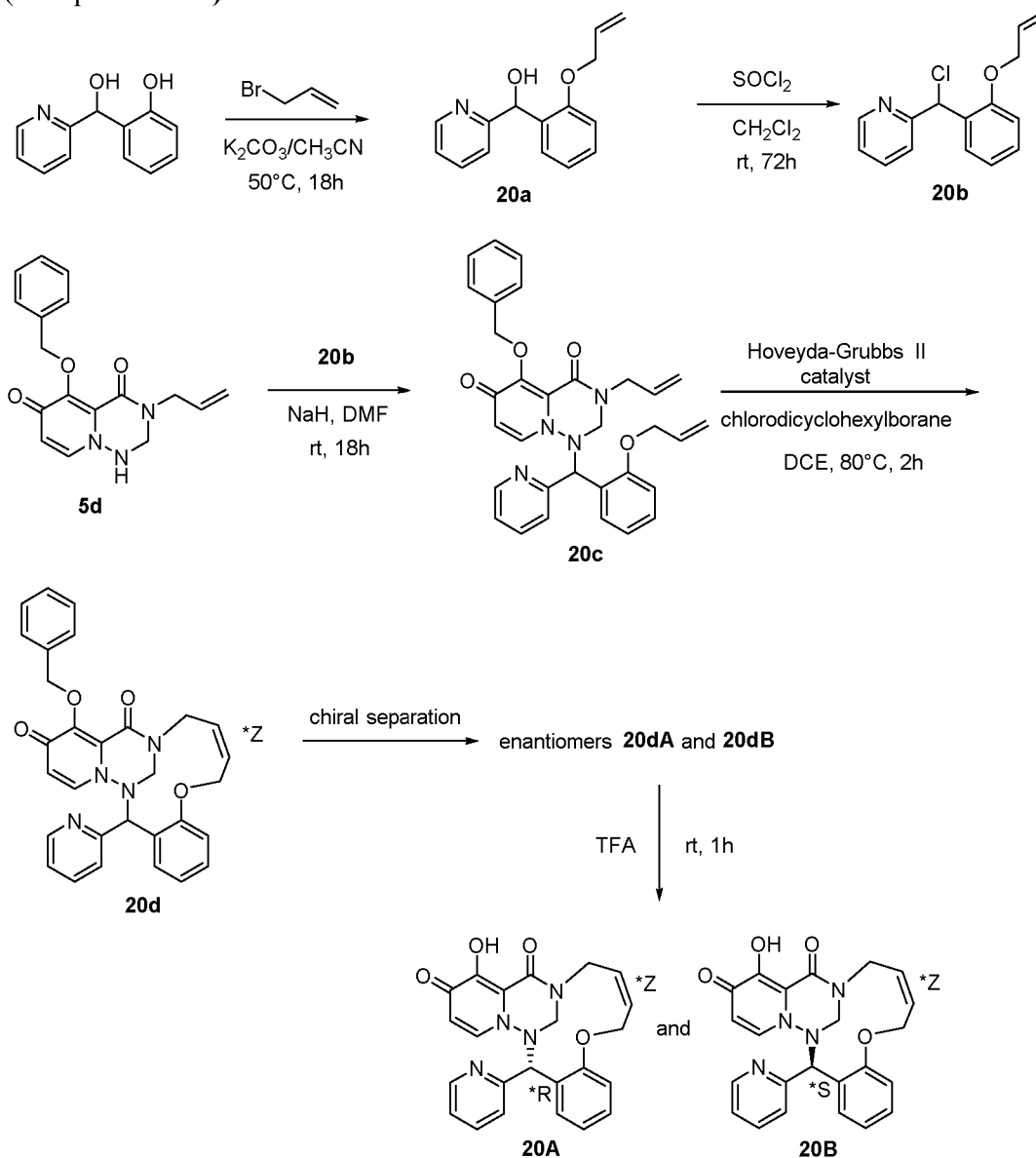
30 Compound 19:

- ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.29 - 2.44 (m, 2 H) 3.19 (br dd, *J*=13.4, 7.8 Hz, 1 H) 4.19 (d, *J*=13.1 Hz, 1 H) 4.30 (br d, *J*=5.1 Hz, 2 H) 4.76 (br dd, *J*=13.4, 6.8 Hz, 1 H) 5.06 (d, *J*=13.6 Hz, 1 H) 5.42 - 5.55 (m, 2 H) 5.60 (s, 1 H) 5.76 (s, 1 H) 5.80 - 5.91 (m, 1 H) 7.00 - 7.22 (m, 7 H) 7.26 - 7.39 (m, 2 H) 8.07 (d, *J*=7.6 Hz, 1 H) 10.32 - 11.90
35 (m, 1 H)

LC/MS (method LC-B): R_t 2.38 min, MH⁺ 430

Example 20: synthesis of (18^{*}*R*,^{*}*Z*)-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **20A**) and (18^{*}*S*,^{*}*Z*)-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

5 (Compound **20B**)



Synthesis of intermediate **20a**:

A mixture of allyl bromide [CAS 106-95-6] (3.1 mL, 36 mmol), 2-(hydroxy(pyridin-2-yl)methyl)phenol [CAS 158839-52-2] (7.2 g, 36 mmol) and K_2CO_3 (15 g, 0.11 mol) in CH_3CN (93 mL) was stirred at 50°C for 18 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μm , 120 g, heptane/EtOAc from 90/10 to 80/20). The pure fractions were

collected and concentrated under reduced pressure to give (2-(allyloxy)phenyl)(pyridin-2-yl)methanol (intermediate **20a**, 2.5 g).

Synthesis of intermediate 20b:

5 2-((2-(allyloxy)phenyl)chloromethyl)pyridine (intermediate **20b**, 1.4 g), used as such in the next step, was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 20c:

10 3-allyl-1-((2-(allyloxy)phenyl)(pyridin-2-yl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **20c**, 550 mg) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 20d:

15 In a sealed tube, a degassed solution of 3-allyl-1-((2-(allyloxy)phenyl)(pyridin-2-yl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **20c**, 500 mg, 0.94 mmol) and chlorodicyclohexylborane (1M) [CAS 36140-1-9] (190 µL, 0.19 mmol) in DCE (64 mL) was stirred at 80°C under N₂ for 1 h. Hoveyda-Grubbs catalyst 2nd generation [CAS 301224-40-8] (120 mg, 0.19 mmol) was added and the mixture was stirred at 80°C for 2 h. SiliaMetS[®] DMT (1.2 g, 0.75 mmol)
20 was added and the mixture was stirred at rt for 18 h. The reaction mixture was filtered through celite[®]. Celite[®] was washed with CH₂Cl₂ and the filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 µm, 12 g, CH₂Cl₂/CH₃OH from 100/0 to 97/3). A second purification was performed via achiral SFC (Stationary phase: NH₂ 5 µm 150 x 30 mm, Mobile phase: 80% CO₂,
25 20% MeOH). The pure fractions were collected and evaporated to dryness to give (**Z*)-12-(benzyloxy)-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **20d**, 45 mg, racemate). The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel[®] OD-H 5 µm 250 x 20 mm, Mobile phase: 70% CO₂, 30% MeOH) to give the first eluted
30 enantiomer **20dA** (17 mg) and the second eluted enantiomer **20dB** (22 mg).

Synthesis of Compound 20A:

(18*R*,**Z*)-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound
35 **20A**, 9 mg) was obtained using the procedure described for compound **5A**.

Compound 20A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.09 - 3.16 (m, 1 H) 4.16 (d, *J*=13.9 Hz, 1 H) 4.26 (br t, *J*=9.3 Hz, 1 H) 4.63 - 4.84 (m, 2 H) 5.04 (d, *J*=13.9 Hz, 1 H) 5.33 - 5.50 (m, 2 H) 5.79 - 5.91 (m, 1 H) 6.00 - 6.21 (m, 1 H) 7.05 (d, *J*=7.9 Hz, 1 H) 7.09 - 7.18 (m, 2 H) 7.20 (br d, *J*=7.9 Hz, 1 H) 7.23 - 7.31 (m, 1 H) 7.31 - 7.43 (m, 1 H) 7.56 (br t, *J*=7.1 Hz, 1 H) 8.06 (br d, *J*=7.6 Hz, 1 H) 8.30 (br d, *J*=4.1 Hz, 1 H)
LC/MS (method LC-A): R_t 2.11 min, MH⁺ 417
[α]_D²⁰: -679.57° (c 0.093, DMF)

10 Synthesis of Compound 20B:

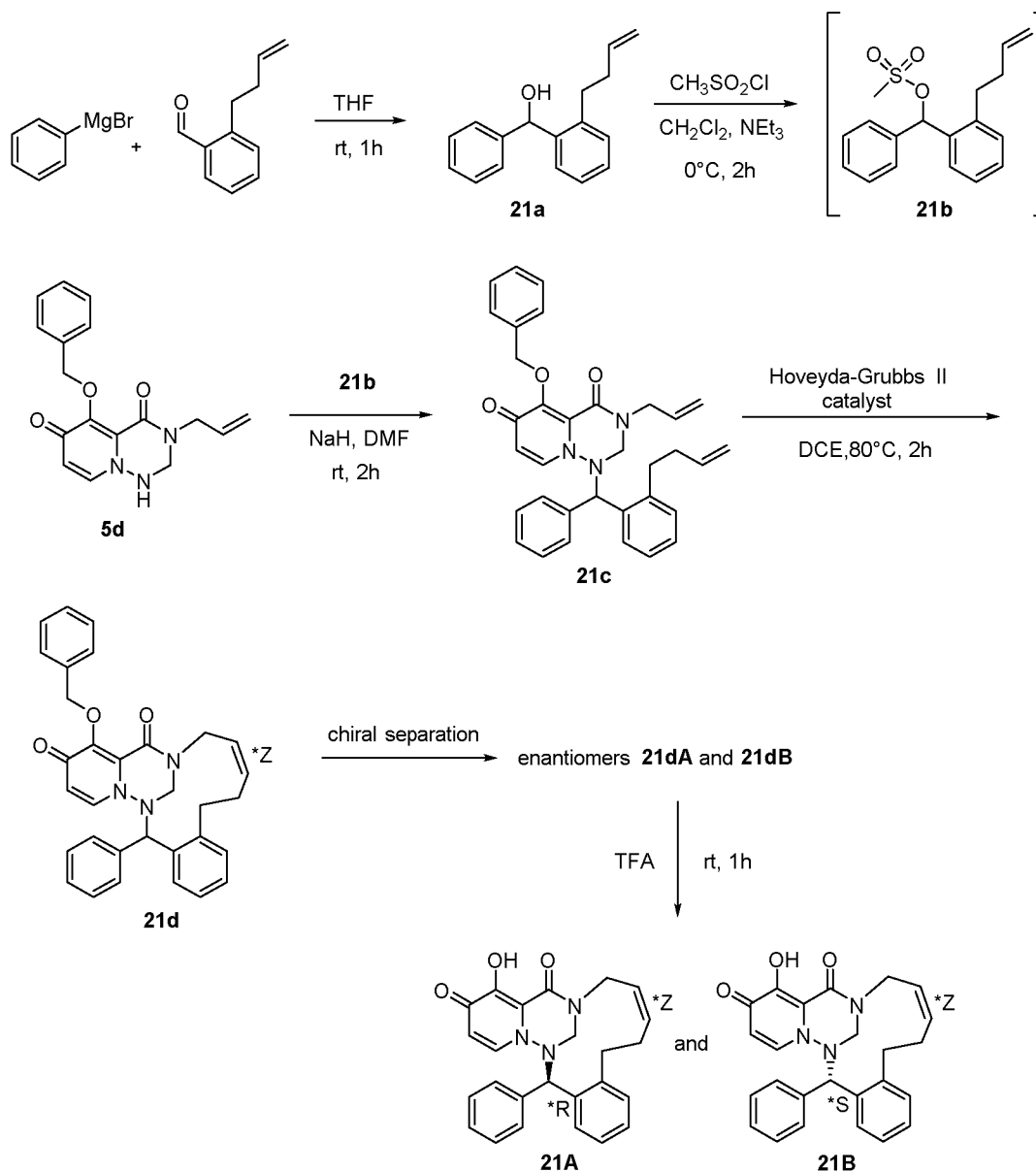
(18**S*,**Z*)-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **20B**, 12 mg) was obtained using the procedure described for compound **5A**.

15 Compound 20B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.98 - 3.16 (m, 1 H) 4.16 (br d, *J*=13.9 Hz, 1 H) 4.26 (br t, *J*=8.5 Hz, 1 H) 4.56 - 4.80 (m, 2 H) 5.03 (br d, *J*=13.6 Hz, 1 H) 5.35 - 5.54 (m, 2 H) 5.69 - 5.94 (m, 1 H) 5.99 - 6.18 (m, 1 H) 7.00 - 7.08 (m, 1 H) 7.10 - 7.23 (m, 3 H) 7.23 - 7.30 (m, 1 H) 7.32 - 7.40 (m, 1 H) 7.56 (br t, *J*=7.3 Hz, 1 H) 8.06 (br d, *J*=7.6 Hz, 1 H) 8.30 (br d, *J*=4.1 Hz, 1 H)
LC/MS (method LC-A): R_t 2.11 min, MH⁺ 417
[α]_D²⁰: +668.13° (c 0.091, DMF)

Example 21: synthesis of (17**R*,**Z*)-4-hydroxy-16-phenyl-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **21A**) and (17**S*,**Z*)-4-hydroxy-16-phenyl-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **21B**)

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Synthesis of intermediate **21a**:

At 0°C under N_2 flow, phenylmagnesium bromide [CAS 100-58-3] (35 mL, 34.89 mmol) was added dropwise to a solution of 2-(but-3-en-1-yl)benzaldehyde [CAS 70576-29-3] (4.3 g, 26.84 mmol) in THF (30 mL). The mixture was stirred under N_2 at rt for 1 h. The reaction was quenched at 0°C with a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO_4 , filtered and the solvent was concentrated under reduced pressure to give (2-(but-3-en-1-yl)phenyl)(phenyl)methanol (intermediate **21a**, 4.2 g).

Synthesis of intermediate 21b:

At 0°C under N₂ flow, methanesulfonyl chloride (974 µL, 12.59 mmol) was added dropwise to a solution of (2-(but-3-en-1-yl)phenyl)(phenyl)methanol (intermediate **21a**, 1.5 g, 6.29 mmol) and NEt₃ (2.62 mL, 18.8 mmol) in CH₂Cl₂ (30 mL). The reaction was stirred at 0°C for 2 h. Water was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give intermediate **21b** (2.1 g), which was used as such in the next step.

10 Synthesis of intermediate 21c:

3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)phenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **21c**, 1.08 g) was obtained using the procedure described for intermediate **5e**.

15 Synthesis of intermediate 21d:

(*Z*)-4-(benzyloxy)-16-phenyl-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **21d**, 455 mg) was obtained using the procedure described for intermediate **5f**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralpak[®] AD-H 5 µm 250 x 30mm, Mobile phase: 65% CO₂, 35% MeOH) to give the first eluted enantiomer **21dA** (215 mg) and the second eluted enantiomer **21dB** (204 mg).

Synthesis of Compound 21A:

(17**R*, **Z*)-4-hydroxy-16-phenyl-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **21A**, 110 mg) was obtained using the procedure described for compound **5A**.

Compound 21A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.94 - 2.06 (m, 1 H) 2.58 - 2.69 (m, 1 H) 3.09 (dd, *J*=13.9, 7.9 Hz, 1 H) 4.28 (d, *J*=13.6 Hz, 1 H) 4.72 (dd, *J*=14.0, 5.2 Hz, 1 H) 5.12 (d, *J*=13.6 Hz, 1 H) 5.19 (s, 1 H) 5.42 - 5.53 (m, 2 H) 5.96 (dt, *J*=15.7, 7.8 Hz, 1 H) 6.93 - 7.29 (m, 7 H) 7.34 (td, *J*=7.4, 0.9 Hz, 1 H) 7.43 (t, *J*=7.1 Hz, 1 H) 8.07 (d, *J*=7.9 Hz, 1 H) (2 protons under DMSO peak)
LC/MS (method LC-A): R_t 2.72 min, MH⁺ 414
[α]_D²⁰: -639.45° (c 0.365, DMF)

Synthesis of Compound 21B:

(17^{*}*S*,^{*}*Z*)-4-hydroxy-16-phenyl-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **21B**, 110 mg) was obtained using the procedure described for compound **5A**.

5

Compound 21B:

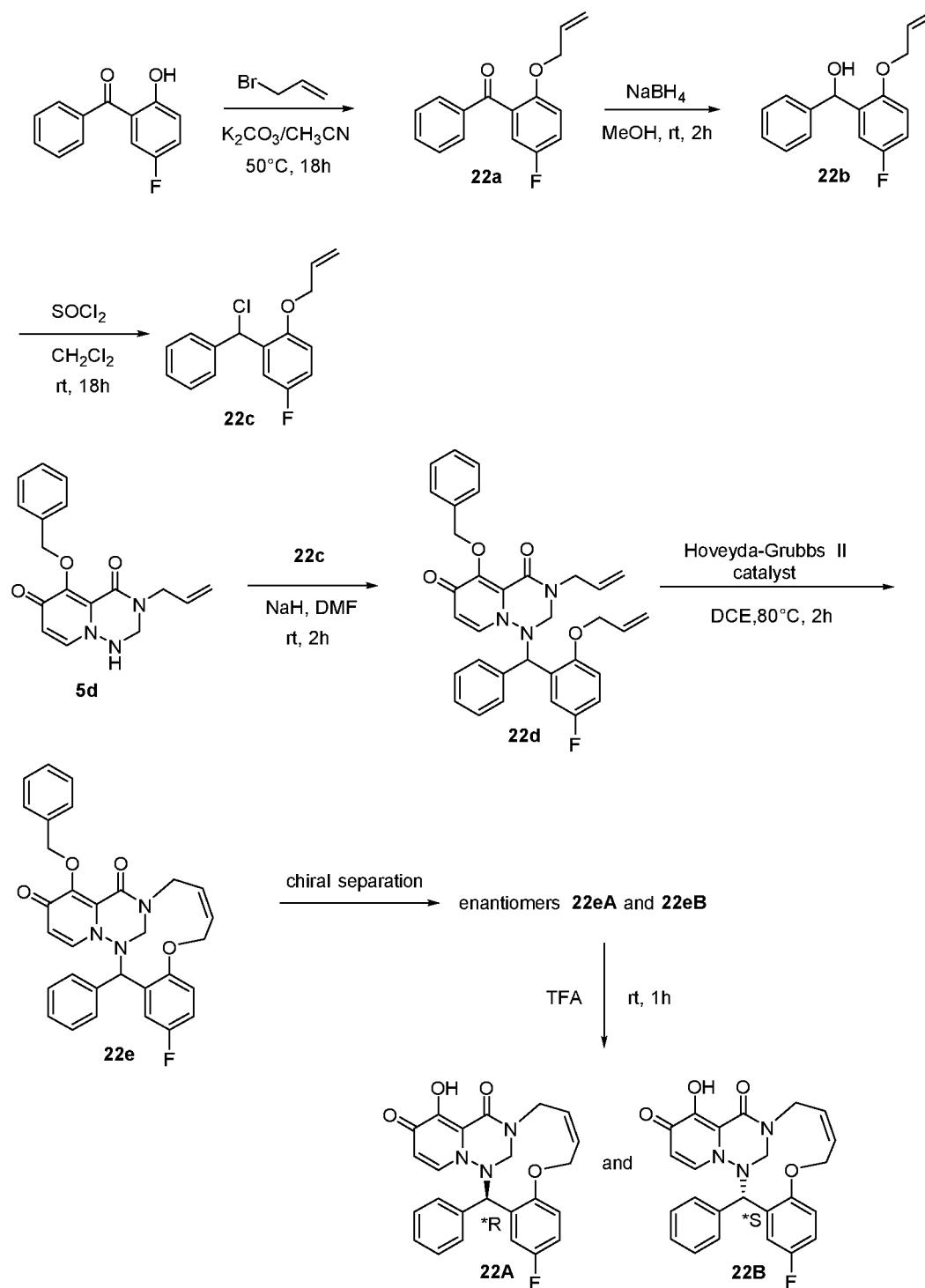
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.94 - 2.06 (m, 1 H) 2.58 - 2.69 (m, 1 H) 3.09 (dd, *J*=14.0, 8.0 Hz, 1 H) 4.28 (d, *J*=13.9 Hz, 1 H) 4.72 (dd, *J*=14.0, 5.2 Hz, 1 H) 5.12 (d, *J*=13.6 Hz, 1 H) 5.19 (s, 1 H) 5.40 - 5.55 (m, 2 H) 5.96 (dt, *J*=15.3, 7.8 Hz, 1 H) 6.91 - 7.30 (m, 7 H) 7.34 (td, *J*=7.4, 0.9 Hz, 1 H) 7.40 - 7.48 (m, 1 H) 8.07 (d, *J*=7.6 Hz, 1 H) (2 protons under DMSO peak)

LC/MS (method LC-A): R_t 2.72 min, MH⁺ 414

[α]_D²⁰: +646.23° (c 0.365, DMF)

- 15 Example 22: synthesis of (18^{*}*R*,*Z*)-2-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **22A**) and (18^{*}*S*,*Z*)-2-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **22B**)

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**Synthesis of intermediate 22a:**

(2-(allyloxy)-5-fluorophenyl)(phenyl)methanone (intermediate **22a**, 2.47 g), used as such in the next step, was obtained using the procedure described for intermediate **20a**.

5

Synthesis of intermediate 22b:

(2-(allyloxy)-5-fluorophenyl)(phenyl)methanol (intermediate **22b**, 2.3 g), used as such in the next step, was obtained using the procedure described for intermediate **11b**.

Synthesis of intermediate 22c:

1-(allyloxy)-2-(chloro(phenyl)methyl)-4-fluorobenzene (intermediate **22c**, 2.4 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 22d:

3-allyl-1-((2-(allyloxy)-5-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **22d**, 2.93 g) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 22e:

(**Z*)-12-(benzyloxy)-2-fluoro-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **22e**, 780 mg) was obtained using the procedure described for intermediate **5f**.

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OJ-H 5 µm 250 x 20mm, Mobile phase: 65% CO₂, 35% MeOH) to give the first eluted enantiomer **22eA** (326 mg) and the second eluted enantiomer **22eB** (340 mg).

Synthesis of Compound 22A:

(18**R,Z*)-2-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **22A**, 145 mg) was obtained using the procedure described for compound **5A**.

Compound 22A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.19 (dd, *J*=13.7, 8.4 Hz, 1 H) 4.30 (d, *J*=13.9 Hz, 2 H) 4.68 - 4.83 (m, 2 H) 5.12 (d, *J*=13.6 Hz, 1 H) 5.28 (br s, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.95 (br s, 1 H) 6.06 - 6.23 (m, 1 H) 7.06 - 7.30 (m, 7 H) 7.33 (br d, *J*=7.6 Hz, 1 H) 7.94 (br d, *J*=8.8 Hz, 1 H) 10.07 - 11.46 (m, 1 H)
LC/MS (method LC-A): R_t 2.47 min, MH⁺ 434
[α]_D²⁰: +645.02° (c 0.291, DMF)

Synthesis of Compound 22B:

(18**S,Z*)-2-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **22B**, 149 mg) was obtained using the procedure described for compound **5B**.

Compound 22B:

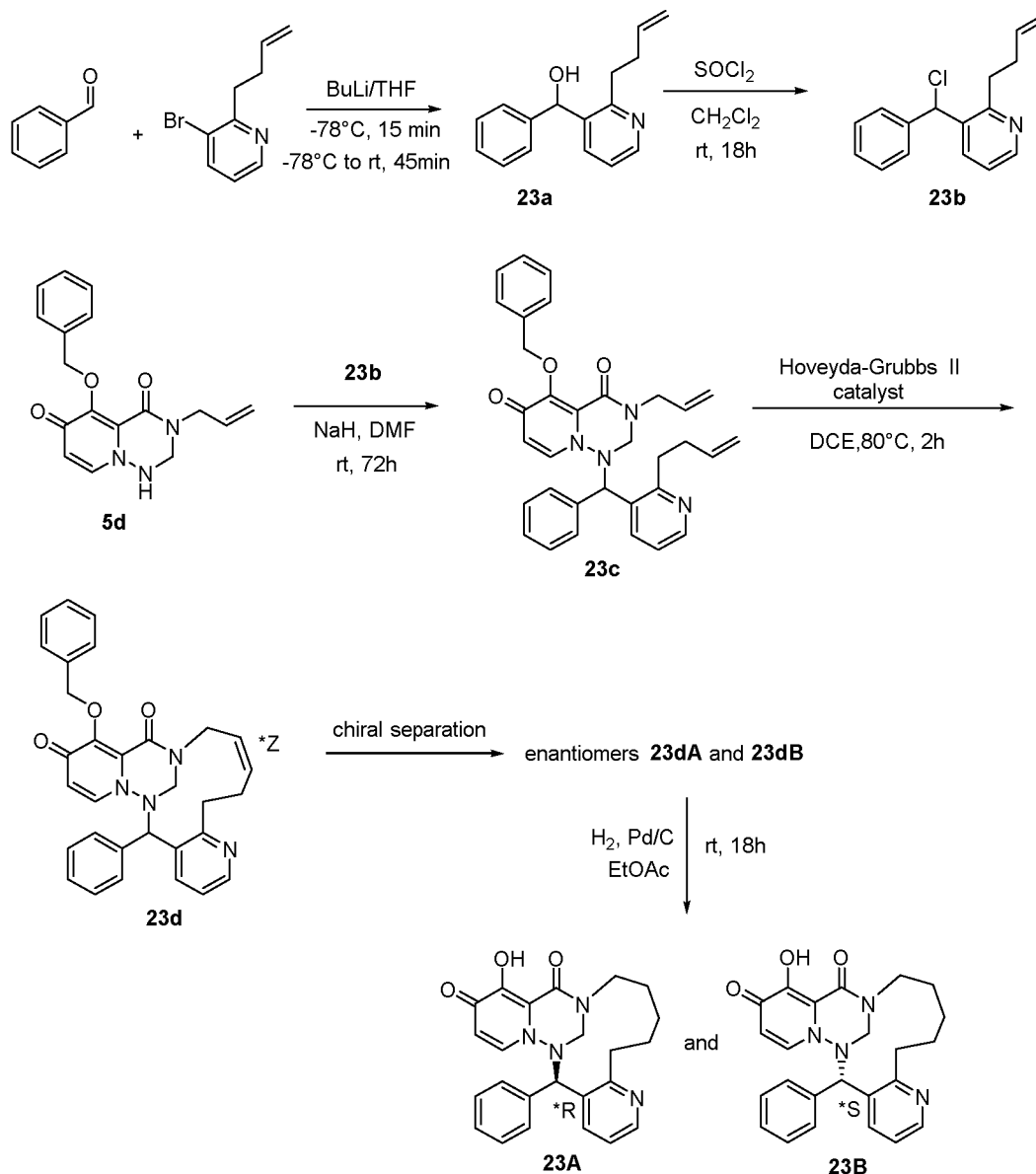
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.19 (dd, *J*=13.6, 8.5 Hz, 1 H) 4.30 (br d, *J*=13.9 Hz, 2 H) 4.68 - 4.83 (m, 2 H) 5.12 (d, *J*=13.9 Hz, 1 H) 5.28 (br s, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.95 (br s, 1 H) 6.07 - 6.22 (m, 1 H) 7.08 - 7.30 (m, 7 H) 7.33 (br d, *J*=7.6 Hz, 1 H) 7.94 (br d, *J*=8.5 Hz, 1 H) 10.48 - 11.25 (m, 1 H)

LC/MS (method LC-A): R_t 2.47 min, MH⁺ 434

[α]_D²⁰: -676.17° (c 0.277, DMF)

Example 23: synthesis of (18**R*)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2-*b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **23A**) and (18**S*)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2-*b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **23B**)

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Synthesis of intermediate 23a:

n-BuLi (1.6 M in hexane) (4.1 mL, 6.6 mmol) was added dropwise to a solution of 3-bromo-2-(but-3-en-1-yl)pyridine [CAS 1309650-05-2] (1.0 g, 4.7 mmol) in dry THF (38 mL) at -78°C . The mixture was stirred 15 min at this temperature, then benzaldehyde [CAS 100-52-7] (0.96 mL, 9.4 mmol) was added dropwise. The mixture was stirred at -78°C for 15 min and then slowly warmed up to rt over 45 min. NH_4Cl 10% aqueous solution was added and the mixture was stirred at rt for 18 h. EtOAc and brine were added and the mixture was extracted with EtOAc twice. The combined organic layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30 μm , 24 g, heptane/EtOAc from 85/15 to 65/35). The pure fractions were collected and concentrated to dryness to give (2-(but-3-en-1-yl)pyridin-3-yl)(phenyl)methanol (intermediate **23a**, 700 mg).

Synthesis of intermediate 23b:

2-(but-3-en-1-yl)-3-(chloro(phenyl)methyl)pyridine (intermediate **23b**, 750 mg) was obtained using the procedure described for intermediate **11c**.

5 Synthesis of intermediate 23c:

3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)pyridin-3-yl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **23c**, 900 mg) was obtained using the procedure described for intermediate **11g**.

10 Synthesis of intermediate 23d:

(*Z)-12-(benzyloxy)-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (intermediate **23d**, 510 mg) was obtained using the procedure described for intermediate **5f**.

The two enantiomers were separated via chiral SFC (Stationary phase: Whelk[®] O1 (*S,S*))

15 5 µm 250 x 21.1 mm, Mobile phase: 60% CO₂, 40% MeOH) to give the first eluted enantiomer **23dA** (190 mg) and the second eluted enantiomer **23dB** (200 mg).

Synthesis of Compound 23A:

(18**R*)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2-

20 *b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **23A**, 22 mg) was obtained using the procedure described for compound **8**.

Compound 23A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.40 - 0.68 (m, 1 H) 1.31 - 1.49 (m, 1 H) 1.49 -
25 1.82 (m, 3 H) 1.87 - 2.06 (m, 1 H) 2.54 - 2.60 (m, 2 H) 2.84-2.94 (m, 1 H) 4.00 (br t, *J*=12.9 Hz, 1 H) 4.27 (br d, *J*=13.9 Hz, 1 H) 5.06 (br d, *J*=13.9 Hz, 1 H) 5.48 (br d, *J*=7.3 Hz, 1 H) 5.60 (s, 1 H) 7.00 (br d, *J*=7.3 Hz, 1 H) 7.19 - 7.55 (m, 6 H) 8.37 (d, *J*=7.9 Hz, 1 H) 8.46 - 8.62 (m, 1 H)

LC/MS (method LC-A): *R*_t 2.07 min, *MH*⁺ 417

30 [*α*]_D²⁰: +395.06° (c 0.162, DMF)

Synthesis of Compound 23B:

(18**S*)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2-

35 *b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **23B**, 22 mg) was obtained using the procedure described for compound **8**.

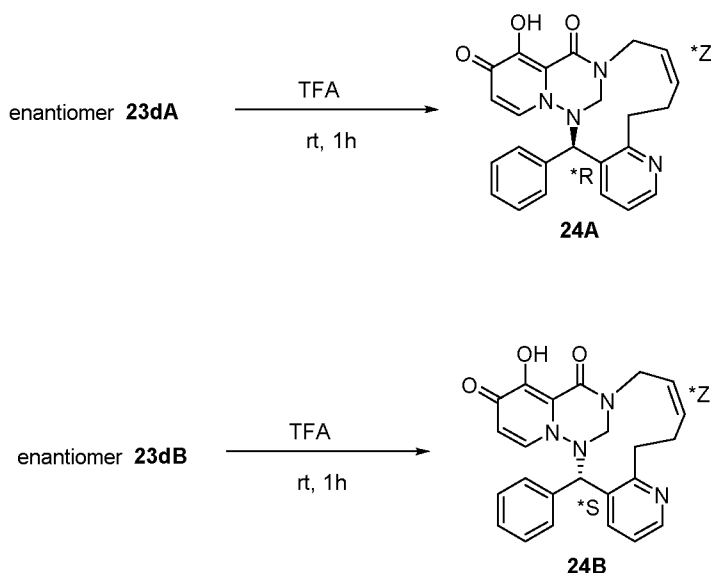
Compound 23B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.49 - 0.60 (m, 1 H) 1.35-1.45 (m, 1 H) 1.48 - 1.87 (m, 3 H) 1.89 - 2.06 (m, 1 H) 2.54 - 2.63 (m, 2 H) 2.84 - 2.95 (m, 1 H) 3.94 - 4.06 (m, 1 H) 4.27 (d, *J*=13.9 Hz, 1 H) 5.06 (br d, *J*=13.9 Hz, 1 H) 5.49 (br d, *J*=7.6 Hz, 1 H) 5.60 (s, 1 H) 7.01 (br d, *J*=7.6 Hz, 1 H) 7.15 - 7.65 (m, 6 H) 8.37 (dd, *J*=7.9, 1.3 Hz, 1 H) 8.55 (dd, *J*=4.7, 1.6 Hz, 1 H)

LC/MS (method LC-A): R_t 2.07 min, MH⁺ 417

[α]_D²⁰: -385.58° (c 0.215, DMF)

- 10 **Example 24:** synthesis of (18^{*R},*Z)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **24A**) and (18^{*S},*Z)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **24B**)

**Synthesis of Compound 24A:**

(18^{*R},*Z)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:2',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **24A**, TFA salt, 115 mg) was obtained using the procedure described for compound **5A**.

Compound 24A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.15 - 2.28 (m, 1 H) 2.59 - 2.84 (m, 3 H) 2.98 - 3.19 (m, 1 H) 4.24 (d, *J*=13.9 Hz, 1 H) 4.67 - 4.84 (m, 1 H) 5.14 (d, *J*=13.9 Hz, 1 H) 5.24 (s, 1 H) 5.52 (d, *J*=7.9 Hz, 1 H) 5.55 - 5.69 (m, 1 H) 6.02 (dt, *J*=15.1, 7.6 Hz, 1 H) 7.00 - 7.46 (m, 6 H) 7.67 (br dd, *J*=7.6, 5.0 Hz, 1 H) 8.53 - 8.83 (m, 2 H)

LC/MS (method LC-A): R_t 2.02 min, MH⁺ 415

$[\alpha]_D^{20}$: +572.76° (c 0.279, DMF)

Synthesis of Compound 24B:

(18*S,*Z)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-
5 b:2',3'-k][1,2,5]triazacyclotridecine-11,13-dione (Compound **24B**, TFA salt, 99 mg) was
obtained using the procedure described for compound **5A**.

Compound 24B:

^1H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.16 - 2.29 (m, 1 H) 2.57 - 2.86 (m, 3 H) 3.07
10 (dd, *J*=14.0, 8.0 Hz, 1 H) 4.24 (d, *J*=13.6 Hz, 1 H) 4.69 - 4.82 (m, 1 H) 5.14 (d, *J*=13.9
Hz, 1 H) 5.24 (s, 1 H) 5.52 (d, *J*=7.9 Hz, 1 H) 5.55 - 5.74 (m, 1 H) 6.02 (dt, *J*=15.3, 7.5
Hz, 1 H) 7.13 - 7.40 (m, 6 H) 7.68 (br dd, *J*=7.6, 5.4 Hz, 1 H) 8.61 - 8.81 (m, 2 H)

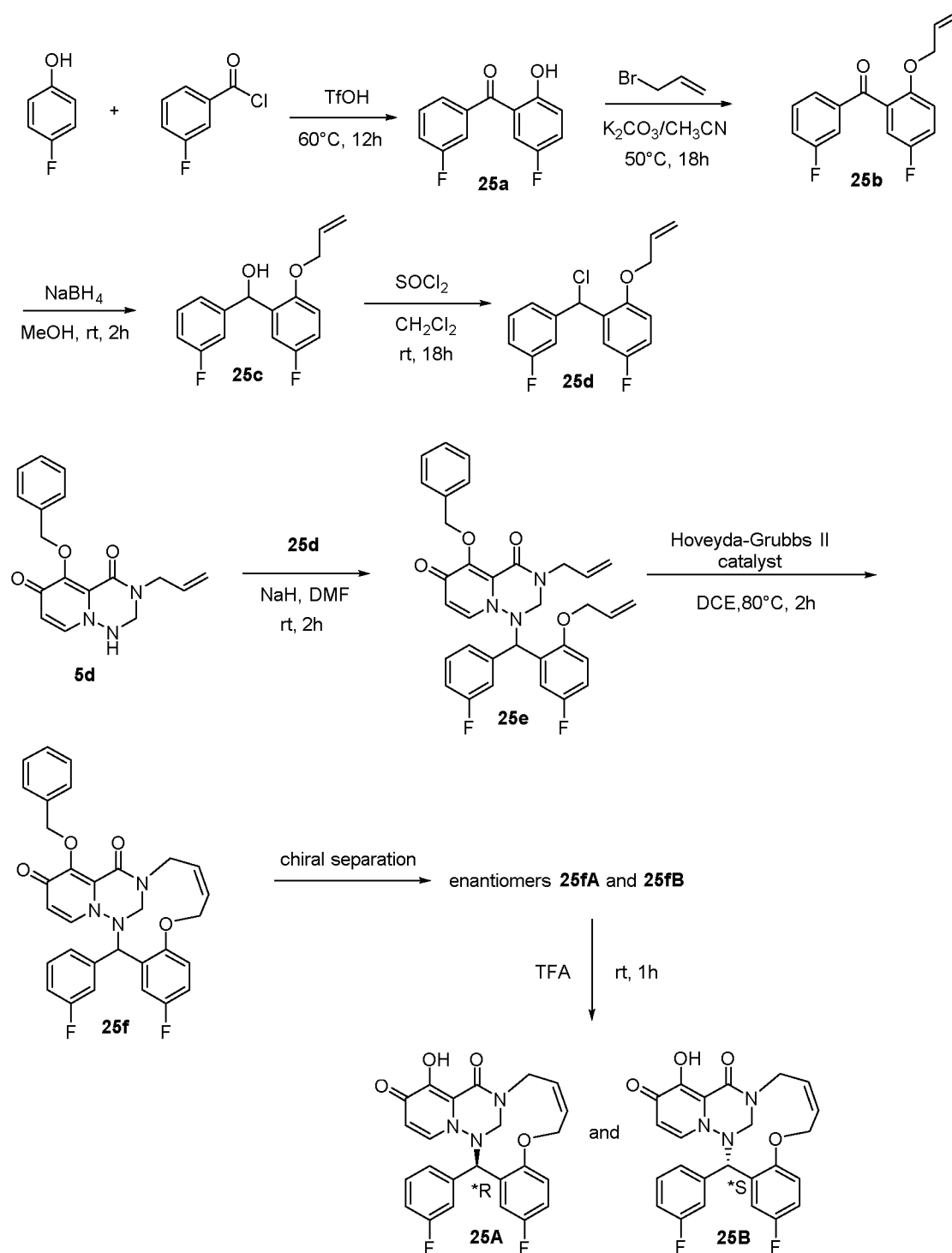
LC/MS (method LC-A): *R*_t 2.02 min, *MH*⁺ 417

$[\alpha]_D^{20}$: -550.53° (c 0.378, DMF)

15

Example 25: synthesis of (18*R,*Z*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-
dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-
11,13-dione (Compound **25A**) and (18*S,*Z*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-
6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-

20 *f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **25B**)



Synthesis of intermediate 25a:

4-fluorophenol [CAS 371-41-5] (1.5 g, 13.38 mmol) and 3-fluorobenzoyl chloride (1.64 mL, 13.38 mmol) were dissolved in triflic acid (50 mL) at 0°C. The reaction mixture was warmed up to rt and stirred at 60°C for 12 h. After cooling down to rt, the mixture was poured into a cold solution of water (250 mL) and EtOAc. The organic layer was

separated, dried over MgSO₄, filtered and concentrated under vacuum to give (5-fluoro-2-hydroxyphenyl)(3-fluorophenyl)methanone (intermediate **25a**, 3.2 g).

Synthesis of intermediate **25f**:

5 (Z)-12-(benzyloxy)-2-fluoro-18-(3-fluorophenyl)-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **25f**, 740 mg) was obtained using the procedures described in example **22**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OJ-H 5 µm 250 x 30 mm, Mobile phase: 75% CO₂, 25% MeOH) to give the first eluted
10 enantiomer **25fA** (313 mg) and the second eluted enantiomer **25fB** (316 mg).

Synthesis of Compound **25A**:

(18**R,Z*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
15 (Compound **25A**, 162 mg) was obtained using the procedure described for compound **5A**.

Compound **25A**:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.18 (br dd, *J*=13.6, 8.1 Hz, 1 H) 4.28 (br d, *J*=13.6 Hz, 2 H) 4.66 - 4.83 (m, 2 H) 5.12 (d, *J*=13.6 Hz, 1 H) 5.30 (br s, 1 H) 5.57 (d, *J*=7.6 Hz, 1 H) 5.95 (br s, 1 H) 6.13 (br s, 1 H) 6.88 - 7.17 (m, 3 H) 7.19 - 7.33 (m, 3 H) 7.44 (br d, *J*=7.6 Hz, 1 H) 7.96 (br d, *J*=9.6 Hz, 1 H)
LC/MS (method LC-A): R_t 2.52 min, MH⁺ 452
[α]_D²⁰: +615.66° (c 0.281, DMF)
25 Chiral HPLC (method HPLC-B): R_t 4.33 min, chiral purity 100%.

Synthesis of Compound **25B**:

(18**S,Z*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
30 (Compound **25B**, 162 mg) was obtained using the procedure described for compound **5B**.

Compound **25B**:

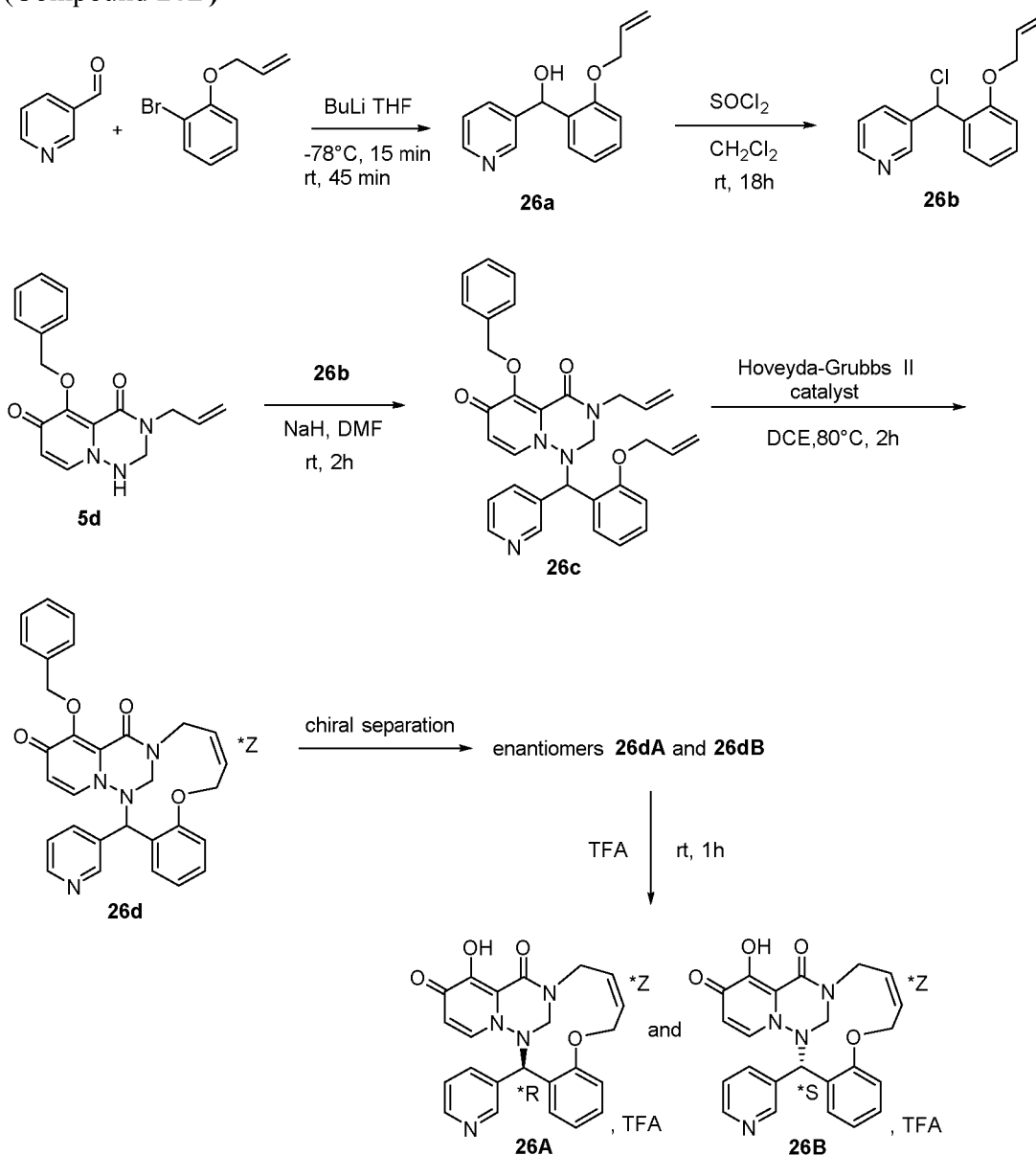
35 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.10 - 3.22 (m, 1 H) 4.28 (br d, *J*=13.1 Hz, 2 H) 4.66 - 4.83 (m, 2 H) 5.12 (br d, *J*=13.6 Hz, 1 H) 5.30 (br s, 1 H) 5.56 (br d, *J*=7.6 Hz, 1 H) 5.95 (br s, 1 H) 6.14 (br s, 1 H) 6.92 - 7.17 (m, 3 H) 7.18 - 7.34 (m, 3 H) 7.44 (br d, *J*=5.1 Hz, 1 H) 7.96 (br d, *J*=9.1 Hz, 1 H) 10.04 - 11.58 (m, 1 H)

LC/MS (method LC-A): R_t 2.52 min, MH^+ 452

$[\alpha]_D^{20}$: -642.59° (c 0.277, DMF)

Chiral HPLC (method HPLC-B): R_t 5.71 min, chiral purity 100%.

- 5 **Example 26:** synthesis of (18**R,*Z*)-12-hydroxy-18-(pyridin-3-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **26A**) and (18**S,*Z*)-12-hydroxy-18-(pyridin-3-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **26B**)



Synthesis of intermediate 26a:

(2-(allyloxy)phenyl)(pyridin-3-yl)methanol (intermediate **26a**, 1.25 g) was obtained using the procedure described for intermediate **23a**.

5 Synthesis of intermediate 26d:

(*Z)-12-(benzyloxy)-18-(pyridin-3-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **26d**, 350 mg) was obtained using the procedures described in example 5 starting from intermediates **26b** (synthesized as **5a**) and **5d**.

- 10 The two enantiomers were separated via chiral SFC (Stationary phase: Whelk[®] O1 (*S,S*) 5 μ m 250 x 21.1 mm, Mobile phase: 40% CO₂, 60% EtOH) to give the first eluted enantiomer **26dA** (93 mg) and the second eluted enantiomer **26dB** (99 mg).

Synthesis of Compound 26A:

- 15 (18**R,*Z*)-12-hydroxy-18-(pyridin-3-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **26A**, TFA salt, 65 mg) was obtained using the procedure described for compound **5A**.

20 Compound 26A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.16 - 3.24 (m, 1 H) 4.12 - 4.40 (m, 2 H) 4.68 - 4.95 (m, 2 H) 5.15 (d, *J*=13.6 Hz, 1 H) 5.39 (br s, 1 H) 5.55 (d, *J*=7.6 Hz, 1 H) 5.88 - 5.98 (m, 1 H) 6.10 - 6.22 (m, 1 H) 7.18 - 7.32 (m, 2 H) 7.32 - 7.53 (m, 3 H) 7.70 (br s, 1 H) 8.14 (br d, *J*=7.6 Hz, 1 H) 8.26 - 8.51 (m, 2 H)

- 25 LC/MS (method LC-A): *R*_t 2.04 min, MH⁺ 417

$[\alpha]_D^{20}$: -673.64° (c 0.129, DMF)

Chiral HPLC (method HPLC-B): *R*_t 10.26 min, chiral purity 100%.

Synthesis of Compound 26B:

- 30 (18**S,*Z*)-12-hydroxy-18-(pyridin-3-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **26B**, TFA salt, 63 mg) was obtained using the procedure described for compound **5B**.

35 Compound 26B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.15 - 3.23 (m, 1 H) 4.16 - 4.52 (m, 2 H) 4.71 - 4.93 (m, 2 H) 5.15 (br d, *J*=13.9 Hz, 1 H) 5.39 (br s, 1 H) 5.55 (br d, *J*=7.6 Hz, 1 H) 5.87

- 5.99 (m, 1 H) 6.10-6.24 (m, 1 H) 7.15 - 7.30 (m, 2 H) 7.30 - 7.54 (m, 3 H) 7.69 (br s, 1 H) 8.14 (br d, $J=7.3$ Hz, 1 H) 8.27 - 8.49 (m, 2 H)

LC/MS (method LC-A): R_t 2.04 min, MH^+ 417

$[\alpha]_D^{20}$: +655.46° (c 0.119, DMF)

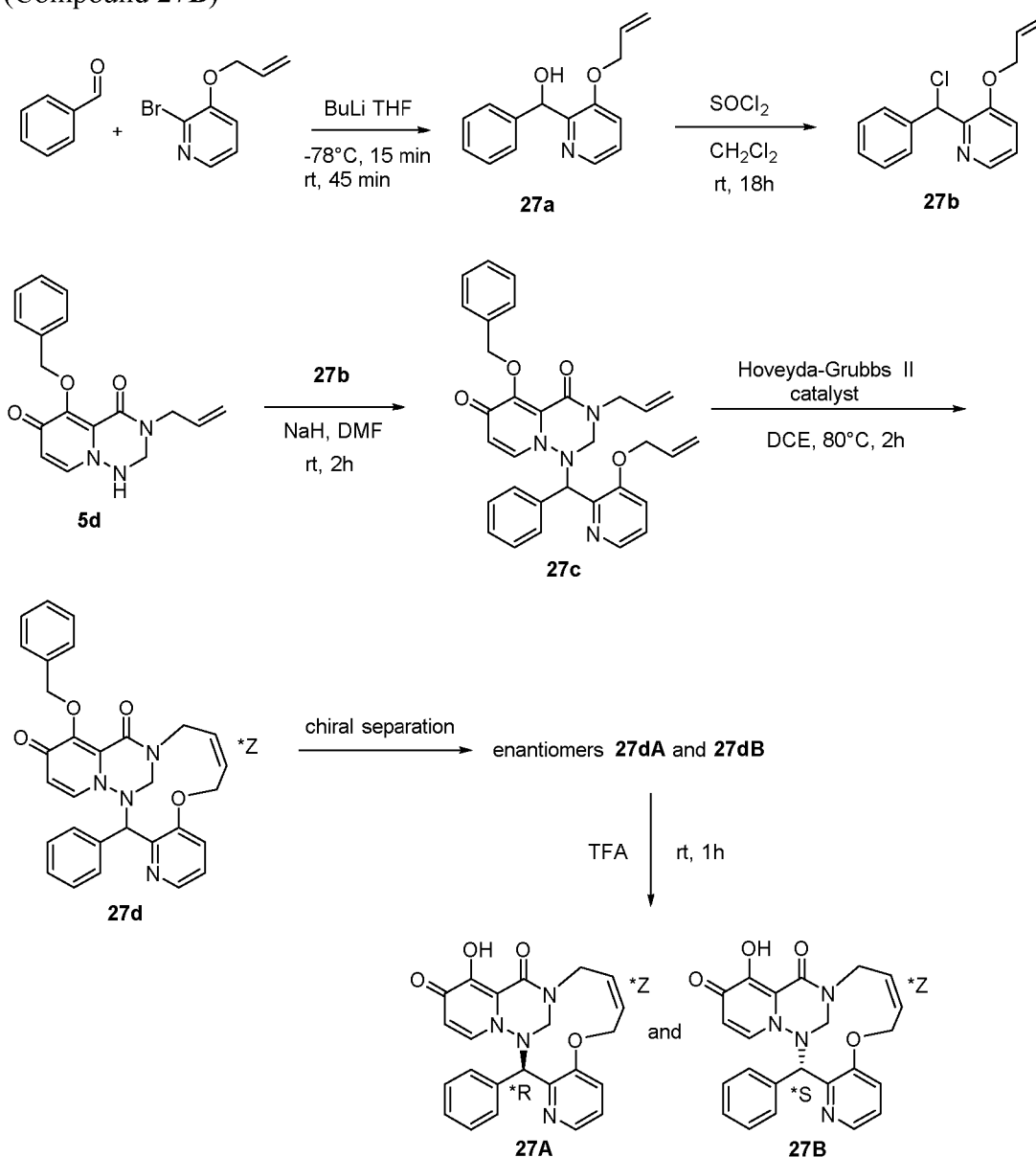
5 Chiral HPLC (method HPLC-B): R_t 7.63 min, chiral purity 100%.

Example 27: synthesis of (18 $^*R$, $^*Z$)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanodipyrido[3,2-*b*:1',2'-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **27A**) and (18 $^*S$, $^*Z$)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-

10 methanodipyrido[3,2-*b*:1',2'-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **27B**)



Synthesis of intermediate 27a:

(3-(allyloxy)pyridin-2-yl)(phenyl)methanol (intermediate **27a**, 1.9 g) was obtained using the procedure described for intermediate **23a**, starting from 3-(allyloxy)-2-bromopyridine [CAS 123552-77-2].

Synthesis of intermediate 27d:

(**Z*)-12-(benzyloxy)-18-phenyl-6,9-dihydro-18*H*-10,17-methanodipyrido[3,2-*b*:1',2'-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **27d**, 0.136 g) was obtained using the procedures described in example **20** starting from intermediates **27b** (synthesized as **5a**) and **5d**.

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel[®] OD-H 5 µm 250 x 30 mm, Mobile phase: 70% CO₂, 30% EtOH) to give the first eluted enantiomer **27dA** (65 mg) and the second eluted enantiomer **27dB** (61 mg).

Synthesis of Compound 27A:

((18**R*,**Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanodipyrido[3,2-*b*:1',2'-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **27A**, TFA salt, 28 mg) was obtained using the procedure described for compound **24A**.

Compound 27A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.13 - 3.21 (m, 1 H) 4.18 (d, *J*=13.9 Hz, 1 H) 4.26 (br t, *J*=10.1 Hz, 1 H) 4.78 (dd, *J*=14.3, 4.6 Hz, 1 H) 4.89 (br dd, *J*=11.0, 6.3 Hz, 1 H) 5.13 (d, *J*=13.9 Hz, 1 H) 5.41 (s, 1 H) 5.47 (d, *J*=7.9 Hz, 1 H) 5.68 - 5.79 (m, 1 H) 6.22 (dt, *J*=15.5, 7.5 Hz, 1 H) 6.98 (d, *J*=7.9 Hz, 1 H) 7.15 - 7.38 (m, 5 H) 7.48 (dd, *J*=8.2, 4.4 Hz, 1 H) 7.69 (d, *J*=8.2 Hz, 1 H) 8.48 - 8.61 (m, 1 H) 11.06 (br s, 1 H)

LC/MS (method LC-A): R_t 2.01 min, MH⁺ 417

[α]_D²⁰: -700.93° (c 0.107, DMF)

Chiral HPLC (method HPLC-B): R_t 6.75 min, chiral purity 100%.

Synthesis of Compound 27B:

((18**S*,**Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanodipyrido[3,2-*b*:1',2'-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **27B**, TFA salt, 31 mg) was obtained using the procedure described for compound **24B**.

Compound 27B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.10 - 3.19 (m, 1 H) 4.18 (d, *J*=13.9 Hz, 1 H) 4.26 (br t, *J*=10.1 Hz, 1 H) 4.78 (dd, *J*=14.5, 4.7 Hz, 1 H) 4.89 (br dd, *J*=11.0, 6.0 Hz, 1

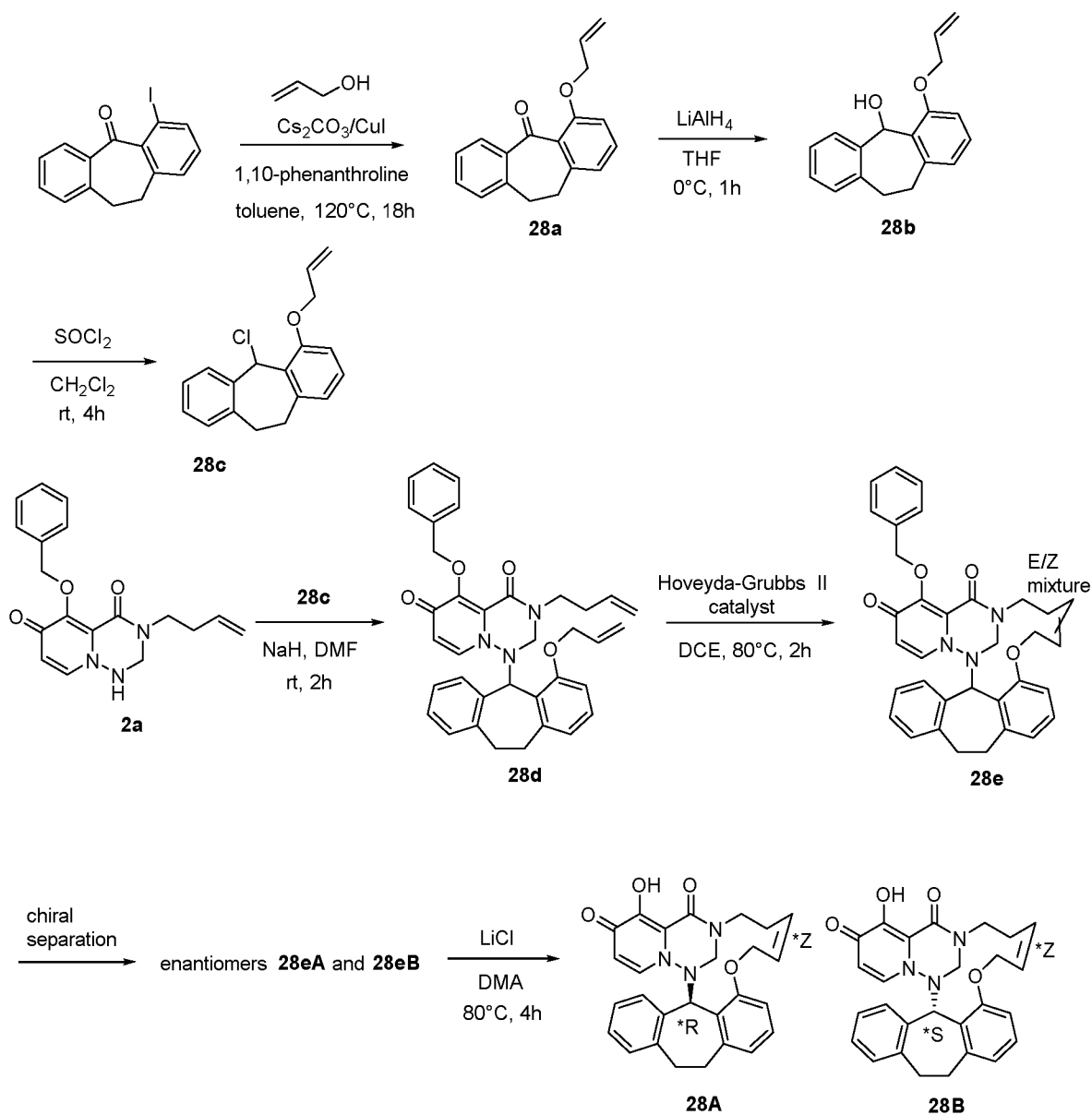
H) 5.13 (d, $J=13.9$ Hz, 1 H) 5.35 (s, 1 H) 5.47 (d, $J=7.6$ Hz, 1 H) 5.64 - 5.86 (m, 1 H) 6.22 (dt, $J=15.3, 7.50$ Hz, 1 H) 6.98 (d, $J=7.60$ Hz, 1 H) 7.10 - 7.43 (m, 5 H) 7.43 - 7.52 (m, 1 H) 7.69 (d, $J=8.2$ Hz, 1 H) 8.57 (d, $J=3.8$ Hz, 1 H)

LC/MS (method LC-A): R_t 2.01 min, MH^+ 417

5 $[\alpha]_D^{20}$: +665.54° (c 0.148, DMF)

Chiral HPLC (method HPLC-B): R_t 5.28 min, chiral purity 100%.

Example 28: synthesis of (Compound **28A**) and (Compound **28B**)



Synthesis of intermediate **28a**:

The reaction was performed in a sealed tube.

A mixture of 4-iodo-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one [CAS 70911-04-5] (7.8 g, 23.34 mmol), 2-propen-1-ol [CAS 107-18-6] (3.19 mL, 46.68 mmol), CuI (444 mg, 2.33 mmol), 1,10-phenanthroline [CAS 5144-89-8] (841 mg, 4.66 mmol) and Cs₂CO₃ (15.2 g, 46.68 mmol) in toluene (20 mL) was stirred vigorously at 120°C for 18 h. The mixture was cooled down to rt and poured into water. The mixture was diluted with EtOAc and then filtered through a pad of celite[®]. The celite[®] was washed with EtOAc. The two layers were separated and the organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 µm, 80 g, Heptane/EtOAc from 90/10 to 80/20). The pure fractions were collected and evaporated to dryness (batch 1, m = 3.4 g). The fractions containing impurities were combined and purified again by flash chromatography over silica gel (15-40 µm, 40 g, Heptane/EtOAc 95/5). The pure fractions were collected and evaporated to dryness (batch 2, m = 0.6 g). The two batches were combined to give 4-(allyloxy)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (intermediate **28a**, 4 g).

Synthesis of intermediate **28b**:

At 0°C under N₂ flow, LiAlH₄ (1M in THF) (17.7 mL, 17.7 mmol) was added dropwise to a solution of 4-(allyloxy)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (intermediate **28a**, 3.9 g, 14.76 mmol) in THF (80 mL). The mixture was stirred at 0°C for 1 h and quenched with EtOAc and diluted with water. The mixture was filtered through celite[®]. The organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give 4-(allyloxy)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (intermediate **28b**, 3.8 g).

Synthesis of intermediate **28c**:

At 0°C, SOCl₂ (1.22 mL, 16.89 mmol) was added dropwise to a solution of 4-(allyloxy)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (intermediate **28b**, 3.75 g, 14.08 mmol) in CH₂Cl₂ (70 mL). The reaction was stirred at 0°C for 30 min and then at rt for 4 h. The mixture was concentrated to dryness, taken up with toluene and concentrated again to give 4-(allyloxy)-5-chloro-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene (intermediate **28c**, 4.2 g), which was used as such in the next step.

Synthesis of intermediate **28d**:

1-(4-(allyloxy)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-yl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **28d**, 5.55 g) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 28e:

Intermediate **28e** (undefined *E/Z* mixture, 620 mg) was obtained using the procedure described for intermediate **5f**. The two enantiomers were separated via chiral SFC (Stationary phase: Whelk-O1 (*S,S*) 5 μ m 250 x 21.2 mm, Mobile phase: 45% CO₂, 55% MeOH) to give the first eluted enantiomer (215 mg, undefined *E/Z* mixture) and the second eluted enantiomer (230 mg, undefined *E/Z* mixture). The first eluted enantiomer was further purified via chiral SFC (Stationary phase: Chiralcel[®] OD-H 5 μ m 250 x 30 mm, Mobile phase: 60% CO₂, 40% MeOH) to give enantiomer **28eA** (139 mg, pure **Z* isomer). The second eluted enantiomer was further purified via chiral SFC (Stationary phase: Chiralpak[®] AD-H 5 μ m 250 x 30 mm, Mobile phase: 60% CO₂, 40% MeOH) to give enantiomer **28eB** (129 mg, pure **Z* isomer).

Synthesis of Compound 28A:

LiCl (54 mg, 1.27 mmol) was added to a solution of **28eA** (139 mg, 0.26 mmol) in DMA (1.44 mL) and the reaction was stirred at 80°C for 4 h. The mixture was cooled to rt and HCl 0.5N in ice was added. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed 3 times with HCl 0.5N, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 μ m, 4 g, CH₂Cl₂/CH₃OH from 99/1 to 97/3). The pure fractions were collected and evaporated to dryness to give, after freeze-drying in 10 mL of CH₃CN/water (2/8), Compound **28A** (65 mg).

Compound 28A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.18 (br d, *J*=14.2 Hz, 1 H) 2.28 - 2.40 (m, 1 H) 2.70 - 2.79 (m, 1 H) 2.85 (br d, *J*=14.2 Hz, 1 H) 2.89 - 3.00 (m, 1 H) 4.18 - 4.32 (m, 2 H) 4.37 - 4.49 (m, 2 H) 4.53 - 4.62 (m, 1 H) 4.82 (d, *J*=12.9 Hz, 1 H) 5.42 (d, *J*=7.6 Hz, 1 H) 5.91 - 6.01 (m, 2 H) 6.05 - 6.14 (m, 1 H) 6.49 (d, *J*=7.6 Hz, 1 H) 6.83 (t, *J*=7.3 Hz, 1 H) 6.92 (d, *J*=7.3 Hz, 1 H) 6.96 (d, *J*=8.2 Hz, 1 H) 7.04 - 7.12 (m, 2 H) 7.13 - 7.20 (m, 1 H) 7.29 (t, *J*=7.9 Hz, 1 H) (1 proton under the peak of water)

LC/MS (method LC-C): R_t 2.92 min, MH⁺ 456

[α]_D²⁰: +291.23° (c, 0.285 DMF)

Chiral HPLC (method HPLC-B): R_t 6.16 min, chiral purity 100%.

Synthesis of Compound 28B:

Compound **28B** (59 mg) was obtained using the procedure described for compound **28A**.

Compound 28B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.19 (br s, 1 H) 2.27 - 2.39 (m, 1 H) 2.71-2.77 (m, 1 H) 2.84 (br d, *J*=14.2 Hz, 1 H) 2.89 - 3.00 (m, 1 H) 4.18 - 4.29 (m, 2 H) 4.36 - 4.48 (m, 2 H) 4.53 - 4.63 (m, 1 H) 4.82 (d, *J*=12.9 Hz, 1 H) 5.41 (d, *J*=7.6 Hz, 1 H) 5.91 - 6.01 (m, 2 H) 6.04 - 6.13 (m, 1 H) 6.49 (d, *J*=7.3 Hz, 1 H) 6.83 (t, *J*=7.1 Hz, 1 H) 6.92 (d, *J*=7.6 Hz, 1 H) 6.96 (d, *J*=8.2 Hz, 1 H) 7.04 - 7.12 (m, 2 H) 7.15 (d, *J*=7.6 Hz, 1 H) 7.28 (t, *J*=7.9 Hz, 1 H) (1 proton under the peak of water)

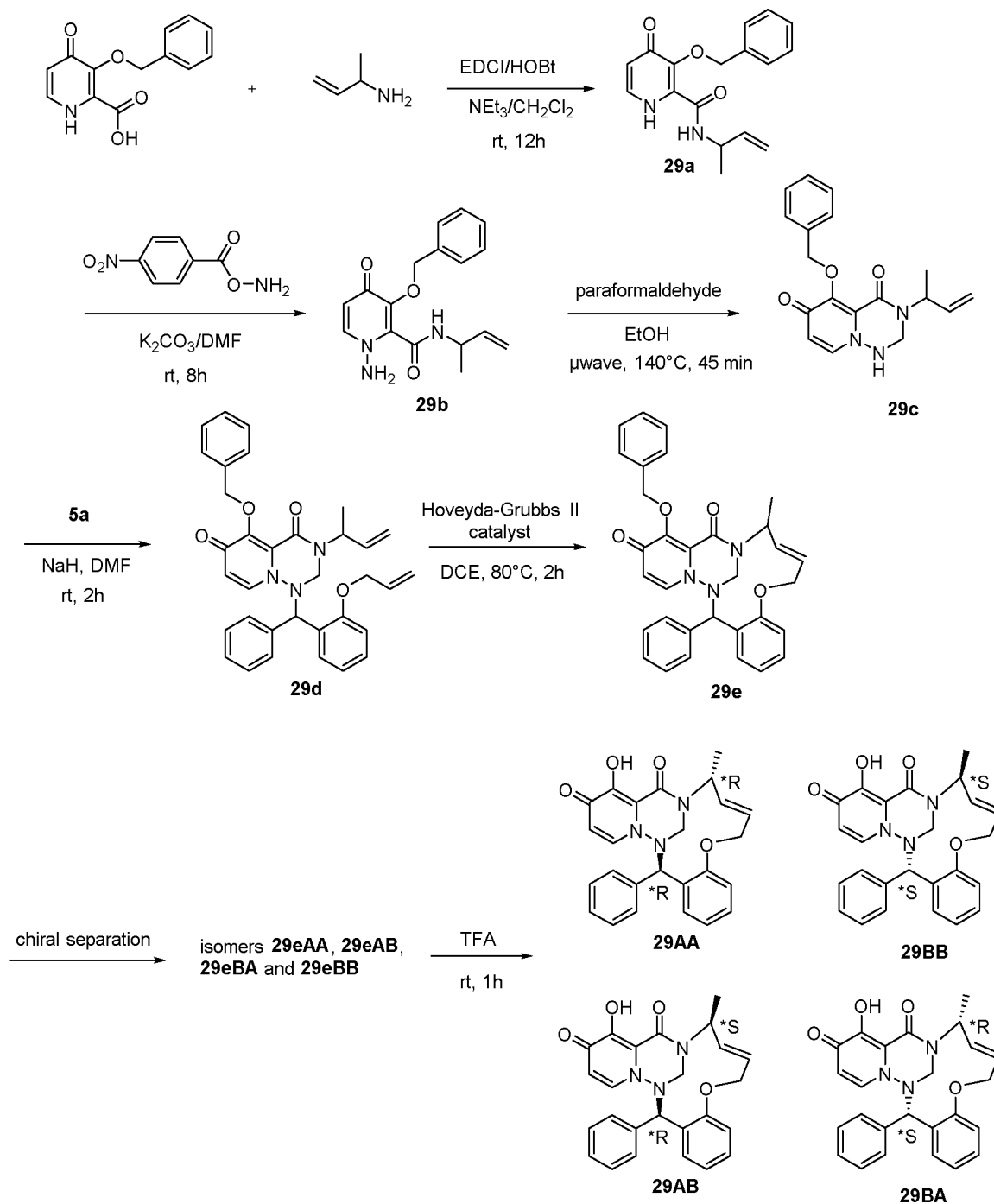
LC/MS (method LC-C): R_t 2.92 min, MH⁺ 456

[α]_D²⁰: -285.33° (c 0.3, DMF)

10 Chiral HPLC (method HPLC-B): R_t 8.52 min, chiral purity 100%.

Example 29: synthesis of (9**R*, 18**R*, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **29AA**), (9**S*, 18**R*, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **29AB**), (9**R*, 18**S*, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **29BA**) and (9**S*, 18**S*, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **29BB**)

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Synthesis of intermediate **29a**:

3-(benzyloxy)-*N*-(but-3-en-2-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **29a**, 2.7 g) was obtained using the procedure described for intermediate **1a** starting from but-3-en-2-amine [CAS 34375-90-1].

Synthesis of intermediate **29b**:

1-amino-3-(benzyloxy)-*N*-(but-3-en-2-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **29b**, 1.77 g) was obtained using the procedure described for intermediate **5c**.

Synthesis of intermediate 29c:

5-(benzyloxy)-3-(but-3-en-2-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **29c**, 1 g) was obtained using the procedure described for intermediate **5d**.

5 Synthesis of intermediate 29d:

1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(but-3-en-2-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **29d**, 740 mg) was obtained using the procedure described for intermediate **5e**.

10 Synthesis of intermediates 29eA and 29eB:

(*E*)-12-(benzyloxy)-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **29e**, 174 mg, 1 diastereoisomer) was obtained using the procedure described for intermediate **5f**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralpak[®] AS-H 5 μ m 250 x 20 mm, Mobile phase: 60% CO₂, 40% EtOH) to give the first eluted enantiomer **29eA** (74 mg) and the second eluted enantiomer **29eB** (75 mg).

Synthesis of Compound 29AA:

20 (9**R*, 18**R*, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **29A**, 31 mg) was obtained using the procedure described for compound **5A**.

Compound 29AA:

25 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.12 (d, *J*=6.9 Hz, 3 H) 4.10 (br t, *J*=10.7 Hz, 1 H) 4.22 (d, *J*=13.6 Hz, 1 H) 4.86 (dd, *J*=11.3, 5.7 Hz, 1 H) 5.02 (d, *J*=13.6 Hz, 1 H) 5.21 (s, 1 H) 5.33 - 5.45 (m, 2 H) 5.48 (d, *J*=7.6 Hz, 1 H) 6.27 (ddd, *J*=14.8, 9.6, 5.5 Hz, 1 H) 7.06 - 7.26 (m, 7 H) 7.33 - 7.39 (m, 1 H) 7.40 - 7.47 (m, 1 H) 8.09 (dd, *J*=7.7, 1.4 Hz, 1 H) 9.92 - 12.00 (m, 1 H)

30 LC/MS (method LC-A): R_t 2.56 min, MH⁺ 430

[α]_D²⁰: +608.99° (c 0.178, DMF)

Chiral HPLC (method HPLC-B): R_t 5.70 min, chiral purity 100%.

Synthesis of Compound 29BB:

35 (9**S*, 18**S*, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **29B**, 27 mg) was obtained using the procedure described for compound **5A**.

Compound 29BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.12 (d, *J*=6.9 Hz, 3 H) 4.10 (t, *J*=10.7 Hz, 1 H) 4.22 (d, *J*=13.6 Hz, 1 H) 4.87 (dd, *J*=11.3, 5.4 Hz, 1 H) 5.02 (d, *J*=13.6 Hz, 1 H) 5.21 (s, 1 H) 5.34 - 5.45 (m, 2 H) 5.48 (d, *J*=7.6 Hz, 1 H) 6.27 (ddd, *J*=14.8, 9.6, 5.5 Hz, 1 H) 7.05 - 7.25 (m, 7 H) 7.33 - 7.40 (m, 1 H) 7.41 - 7.47 (m, 1 H) 8.09 (dd, *J*=7.7, 1.4 Hz, 1 H) 10.34 - 11.93 (m, 1 H)

LC/MS (method LC-A): R_t 2.56 min, MH⁺ 430

[α]_D²⁰: -608.94° (c 0.179, DMF)

Chiral HPLC (method HPLC-B): R_t 6.68 min, chiral purity 100%.

Synthesis of Compound 29AB:

(9*S, 18*R, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound 29A, 31 mg) was obtained using the procedure described for compound 5A.

Compound 29AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.74 (d, *J*=6.9 Hz, 3 H) 3.65 - 3.73 (m, 1 H) 4.17 (d, *J*=13.9 Hz, 1 H) 4.49 - 4.56 (m, 1 H) 4.58 (br t, *J*=10.1 Hz, 1 H) 5.14 (d, *J*=13.9 Hz, 1 H) 5.44 (s, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.71 - 5.85 (m, 1 H) 6.37 - 6.48 (m, 1 H) 7.06 - 7.21 (m, 5 H) 7.26 (d, *J*=7.9 Hz, 1 H) 7.31 - 7.37 (m, 2 H) 7.36 - 7.43 (m, 1 H) 8.14 (dd, *J*=7.88, 1.26 Hz, 1 H) 10.09 - 10.66 (m, 1 H).

LC/MS (method LC-C): R_t 2.66 min, MH⁺ 430

[α]_D²⁰: -737.35° (c 0.166, DMF)

Chiral HPLC (method HPLC-A): R_t 7.59 min, chiral purity 100%.

Synthesis of Compound 29BA:

(9*R, 18*S, *E*)-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound 29A, 31 mg) was obtained using the procedure described for compound 5A.

Compound 29BA:

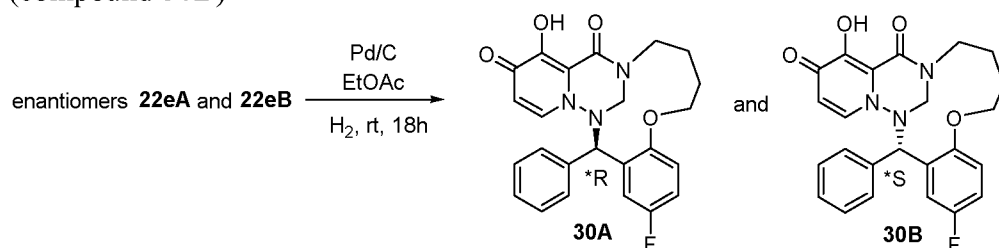
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.74 (d, *J*=6.9 Hz, 3 H) 3.64 - 3.77 (m, 1 H) 4.17 (d, *J*=13.9 Hz, 1 H) 4.49 - 4.63 (m, 2 H) 5.16 (d, *J*=13.87 Hz, 1 H) 5.43 - 5.50 (m, 2 H) 5.73 - 5.90 (m, 1 H) 6.42 (br dd, *J*=15.29, 9.93 Hz, 1 H) 7.06 - 7.20 (m, 5 H) 7.26 (d, *J*=7.88 Hz, 1 H) 7.30 - 7.36 (m, 2 H) 7.36 - 7.45 (m, 1 H) 8.14 (d, *J*=6.62 Hz, 1 H) 10.05 - 10.89 (m, 1 H)

LC/MS (method LC-C): R_t 2.66 min, MH⁺ 430

[α]_D²⁰: +728.18° (c 0.22, DMF)

Chiral HPLC (method HPLC-A): R_t 5.18 min, chiral purity 100%.

Example 30: synthesis of (18^{*}*R*)-2-fluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **30A**) and (18^{*}*S*)-2-fluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **30B**)



Synthesis of Compound 30A:

(18^{*}*R*)-2-fluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **30A**, 24 mg) was obtained using the procedure described for compound **8** starting from intermediate **22eA**.

Compound 30A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.12 (q, *J*=12.4 Hz, 1 H) 1.52 - 1.65 (m, 1 H) 1.75 - 1.97 (m, 2 H) 2.61 - 2.69 (m, 1 H) 4.05 (br t, *J*=12.6 Hz, 1 H) 4.13 (t, *J*=11.5 Hz, 1 H) 4.32 - 4.42 (m, 2 H) 5.02 (d, *J*=13.6 Hz, 1 H) 5.52 (d, *J*=7.9 Hz, 1 H) 5.86 (s, 1 H) 7.15 - 7.43 (m, 8 H) 7.81 (dd, *J*=9.3, 3.0 Hz, 1 H) 11.37 (br s, 1 H)

LC/MS (method LC-C): *R*_t 2.61 min, *MH*⁺ 436

[α]_D²⁰: +314.16° (c 0.113, DMF)

Chiral HPLC (method HPLC-B): *R*_t 7.86 min, chiral purity 100%.

Synthesis of Compound 30B:

(18^{*}*S*)-2-fluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **30B**, 28 mg) was obtained using the procedure described for compound **8** starting from intermediate **22eB**.

Compound 30B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.04 - 1.18 (m, 1 H) 1.52 - 1.67 (m, 1 H) 1.74 - 1.99 (m, 2 H) 2.61 - 2.70 (m, 1 H) 4.05 (br t, *J*=12.8 Hz, 1 H) 4.13 (br t, *J*=11.3 Hz, 1 H)

4.31 - 4.42 (m, 2 H) 5.02 (d, $J=13.6$ Hz, 1 H) 5.52 (d, $J=7.9$ Hz, 1 H) 5.86 (s, 1 H) 7.15 - 7.45 (m, 8 H) 7.81 (dd, $J=9.3, 2.7$ Hz, 1 H) 11.36 (br s, 1 H)

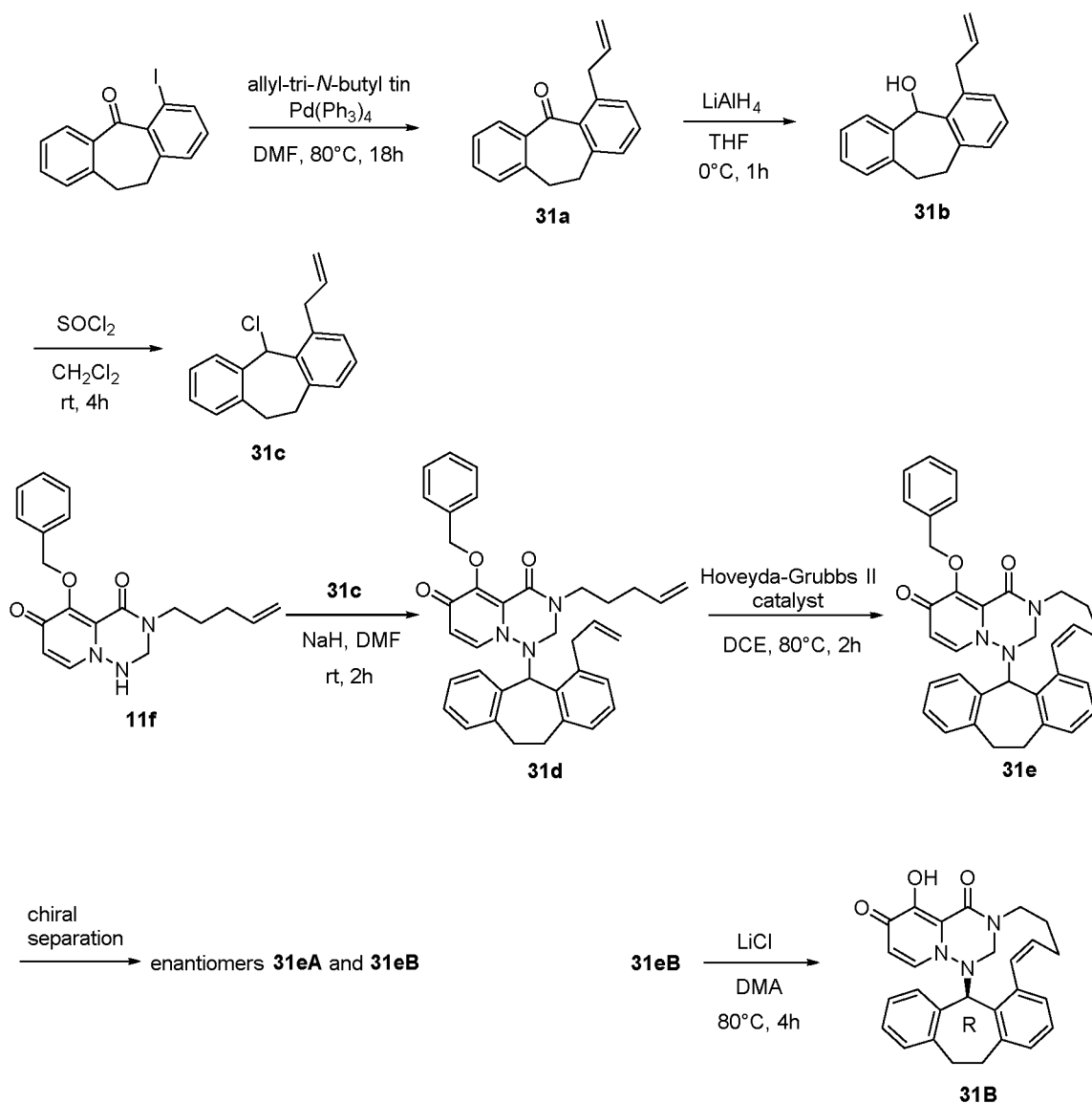
LC/MS (method LC-C): R_t 2.61 min, MH^+ 436

$[\alpha]_D^{20}$: -312.59° (c 0.143, DMF)

5 Chiral HPLC (method HPLC-B): R_t 4.76 min, chiral purity 100%.

Example 31: synthesis of (19*bR,Z*)-4-hydroxy-8,9,15,19*b*-tetrahydro-7*H*,14*H*-13,12-(epi*prop*[1]en[1]yl[3]ylidene)-6,20-methanobenzo[3,4]cyclohepta[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **31B**)

10



Synthesis of intermediate **31a**:

4-allyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (intermediate **31a**, 1.24 g) was obtained using the procedure described for intermediate **11a**.

15

Synthesis of intermediate 31b:

4-allyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (intermediate **31b**, 1.29 g) was obtained using the procedure described for intermediate **28b**.

5 Synthesis of intermediate 31c:

4-allyl-5-chloro-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene (intermediate **31c**, 1.27 g) was obtained using the procedure described for intermediate **28c**.

Synthesis of intermediate 31d:

10 1-(4-allyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-yl)-5-(benzyloxy)-3-(pent-4-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **31d**, 1.07 g) was obtained using the procedure described for intermediate **28d** starting from intermediate **11f**.

15 Synthesis of intermediate 31e:

Intermediate **31e** (138 mg, racemate of the *Z* isomer) was obtained using the procedure described for intermediate **5f**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralpak[®] AS-H 5 μ m 250 x 20 mm, Mobile phase: 70% CO₂, 30% MeOH) to give the first eluted enantiomer **31eA** (68 mg) and the second eluted
20 enantiomer **31eB** (63 mg).

Synthesis of Compound 31B:

(19*bR,Z*)-4-hydroxy-8,9,15,19*b*-tetrahydro-7*H*,14*H*-13,12-(epiprop[1]en[1]yl[3]ylidene)-6,20-methanobenzo[3,4]cyclohepta[1,2-*l*]pyrido[1,2-
25 *b*][1,2,5]triazacyclotridecine-3,5-dione (compound **31B**, 20 mg) was obtained using the procedure described for compound **28A**.

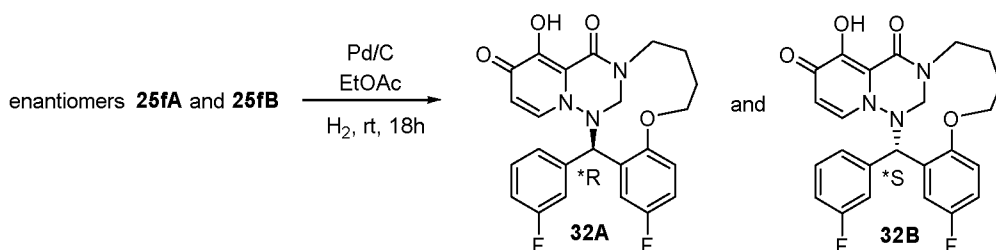
Compound 31B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.50 - 1.64 (m, 1 H) 1.92 - 2.22 (m, 3 H) 2.53 -
30 2.65 (m, 1 H) 2.73 (dt, *J*=14.1, 4.3 Hz, 1 H) 2.90 (ddd, *J*=17.8, 13.1, 5.0 Hz, 1 H) 3.45 - 3.57 (m, 1 H) 3.62 - 3.74 (m, 1 H) 3.98 (d, *J*=12.9 Hz, 1 H) 4.22 (td, *J*=13.6, 5.0 Hz, 1 H) 4.78 (d, *J*=12.9 Hz, 1 H) 5.34 (s, 1 H) 5.40 (d, *J*=7.9 Hz, 1 H) 5.87 (td, *J*=10.5, 4.9 Hz, 1 H) 6.33 (d, *J*=11.0 Hz, 1 H) 6.50 (d, *J*=7.6 Hz, 1 H) 6.78 (d, *J*=7.6 Hz, 1 H) 6.83 (t, *J*=7.3 Hz, 1 H) 6.91 (d, *J*=6.9 Hz, 1 H) 7.07 - 7.18 (m, 2 H) 7.20 - 7.28 (m, 2 H) 11.82
35 (br s, 1 H)

LC/MS (method LC-C): R_t 3.18 min, MH⁺ 440

[α]_D²⁰: -206.93° (c 0.202, DMF)

- Example 32:** synthesis of (18*R*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **32A**) and (18*S*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **32B**)



Synthesis of Compound 32A:

- (18*R*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **32A**, 24 mg) was obtained using the procedure described for compound **8** starting from intermediate **25fA**.

Compound 32A:

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.96 - 1.09 (m, 1 H) 1.51 (br d, *J*=9.8 Hz, 1 H) 1.68 - 1.90 (m, 2 H) 2.54 - 2.62 (m, 1 H) 3.98 (br t, *J*=12.9 Hz, 1 H) 4.06 (br t, *J*=11.2 Hz, 1 H) 4.23 - 4.36 (m, 2 H) 4.96 (d, *J*=13.6 Hz, 1 H) 5.54 (d, *J*=7.6 Hz, 1 H) 5.83 (s, 1 H) 6.98 - 7.34 (m, 7 H) 7.78 (dd, *J*=9.3, 2.7 Hz, 1 H) 11.42 (s, 1 H)
- LC/MS (method LC-C): *R*_t 2.66 min, *MH*⁺ 454
- [α]_D²⁰: +261.02° (c 0.118, DMF)
- Chiral HPLC (method HPLC-B): *R*_t 4.19 min, chiral purity 100%.

Synthesis of Compound 32B:

- (18*S*)-2-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,7,8,9-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **32B**, 16 mg) was obtained using the procedure described for compound **8** starting from intermediate **25fB**.

Compound 32B:

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.11 (m, 1 H) 1.51 (br d, *J*=10.7 Hz, 1 H) 1.68 - 1.91 (m, 2 H) 2.55 - 2.58 (m, 1 H) 3.98 (br t, *J*=12.9 Hz, 1 H) 4.06 (br t, *J*=11.3

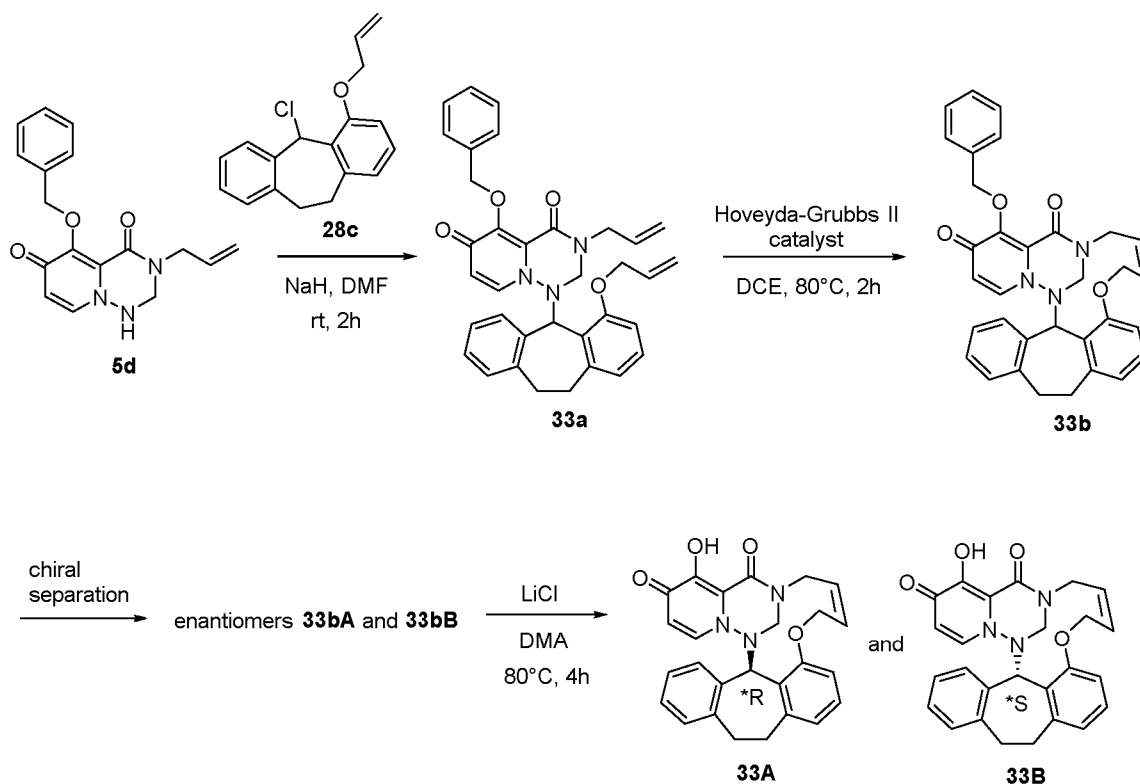
Hz, 1 H) 4.22 - 4.38 (m, 2 H) 4.95 (br d, $J=13.6$ Hz, 1 H) 5.53 (br d, $J=7.9$ Hz, 1 H) 5.83 (s, 1 H) 6.94 - 7.38 (m, 7 H) 7.78 (dd, $J=9.3, 2.4$ Hz, 1 H) 11.32 (br s, 1 H)

LC/MS (method LC-C): R_t 2.66 min, MH^+ 454

$[\alpha]_D^{20}$: -297.35° (c 0.113, DMF)

5 Chiral HPLC (method HPLC-B): R_t 8.38 min, chiral purity 100%.

10 **Example 33**: synthesis of (19*b***R,Z*)-4-hydroxy-7,10,15,19*b*-tetrahydro-14*H*-13,12-(epi-*prop*[1]en[1]yl[3]ylidene)-6,20-methanobenzo[3,4]cyclohepta[1,2-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-3,5-dione (Compound **33A**) and (19*b***S,Z*)-4-hydroxy-7,10,15,19*b*-tetrahydro-14*H*-13,12-(epi-*prop*[1]en[1]yl[3]ylidene)-6,20-methanobenzo[3,4]cyclohepta[1,2-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-3,5-dione (Compound **33B**)



Synthesis of intermediate **33a**:

3-allyl-1-(4-(allyloxy)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-yl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **33a**, 3.1 g) was obtained using the procedure described for intermediate **5e** starting from intermediate **5d**.

Synthesis of intermediate 33b:

(*Z*)-4-(benzyloxy)-7,10,15,19*b*-tetrahydro-14*H*-13,12-(epi-*prop*[1]*en*[1]*yl*[3]*ylidene*)-6,20-methanobenzo[3,4]cyclohepta[1,2-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-3,5-dione (intermediate **33b**, 117 mg) was obtained using the procedure described for intermediate **5f**. A second purification was done via reverse phase (Stationary phase: YMC-actus Triart C18 10 μ m 30 x 150mm, Mobile phase: Gradient from 55% NH_4HCO_3 0.2% , 45% CH_3CN to 35% NH_4HCO_3 0.2% , 65% CH_3CN).

The two enantiomers were separated via chiral SFC (Stationary phase: Whelk-O1 (*S,S*) 5 μ m 250 x 21.2mm, Mobile phase: 45% CO_2 , 55% MeOH) to give the first eluted enantiomer **33bA** (42 mg) and the second eluted enantiomer **33bB** (49 mg).

Synthesis of Compound 33A:

(19*b***R,Z*)-4-hydroxy-7,10,15,19*b*-tetrahydro-14*H*-13,12-(epi-*prop*[1]*en*[1]*yl*[3]*ylidene*)-6,20-methanobenzo[3,4]cyclohepta[1,2-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-3,5-dione (Compound **33A**, 22 mg) was obtained using the procedure described for compound **28A**.

Compound 33A:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 2.77 - 2.85 (m, 1 H) 2.95 (ddd, $J=16.9$, 12.8, 3.8 Hz, 1 H) 3.61 (dt, $J=17.1$, 4.5 Hz, 1 H) 3.78 (br dd, $J=13.4$, 8.4 Hz, 1 H) 4.08 - 4.20 (m, 2 H) 4.26 (d, $J=12.9$ Hz, 1 H) 4.61 (dd, $J=10.7$, 6.6 Hz, 1 H) 4.75 (dd, $J=10.6$, 6.8 Hz, 1 H) 4.97 (d, $J=13.2$ Hz, 1 H) 5.44 (d, $J=7.9$ Hz, 1 H) 5.94 (s, 1 H) 6.30 - 6.37 (m, 1 H) 6.39 - 6.47 (m, 1 H) 6.51 (d, $J=7.6$ Hz, 1 H) 6.81 - 6.90 (m, 1 H) 6.95 (d, $J=7.3$ Hz, 1 H) 7.04 - 7.11 (m, 2 H) 7.12 - 7.22 (m, 2 H) 7.32 (t, $J=7.9$ Hz, 1 H)

LC/MS (method LC-C): R_t 2.80 min, MH^+ 442

$[\alpha]_D^{20}$: +307.89° (c 0.190, DMF)

Chiral HPLC (method HPLC-B): R_t 5.31 min, chiral purity 100%.

Synthesis of Compound 33B:

(19*b***S,Z*)-4-hydroxy-7,10,15,19*b*-tetrahydro-14*H*-13,12-(epi-*prop*[1]*en*[1]*yl*[3]*ylidene*)-6,20-methanobenzo[3,4]cyclohepta[1,2-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-3,5-dione (Compound **33B**, 20 mg) was obtained using the procedure described for compound **28A**.

Compound 33B:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 2.77 - 2.85 (m, 1 H) 2.94 (ddd, $J=16.9$, 12.8, 3.8 Hz, 1 H) 3.60 (dt, $J=17.2$, 4.7 Hz, 1 H) 3.77 (br dd, $J=13.6$, 8.2 Hz, 1 H) 4.08 - 4.18 (m,

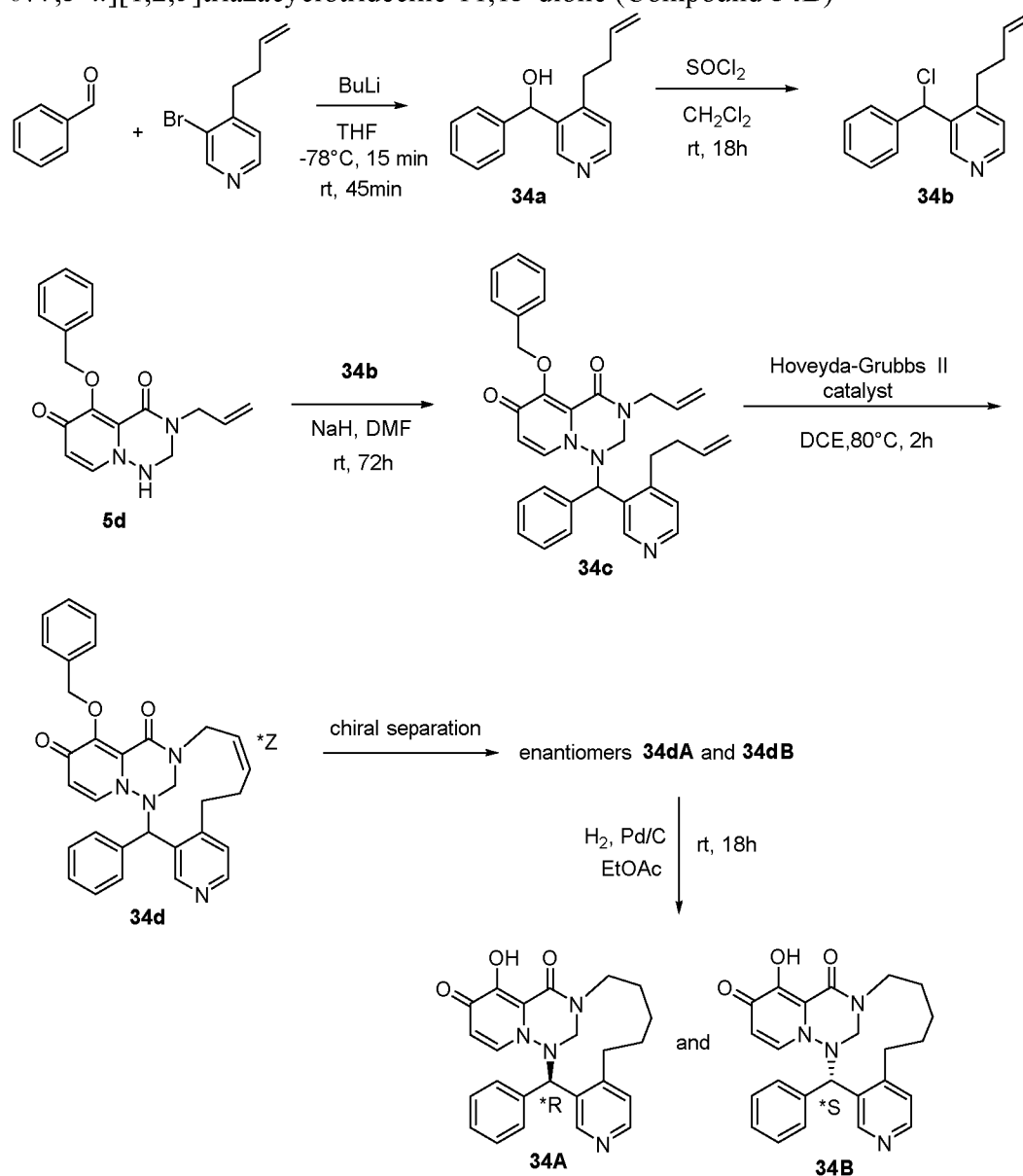
2 H) 4.25 (d, $J=12.9$ Hz, 1 H) 4.60 (dd, $J=10.7$, 6.6 Hz, 1 H) 4.74 (dd, $J=10.7$, 6.6 Hz, 1 H) 4.96 (d, $J=12.9$ Hz, 1 H) 5.43 (d, $J=7.9$ Hz, 1 H) 5.93 (s, 1 H) 6.33 (dt, $J=10.6$, 6.5 Hz, 1 H) 6.38 - 6.46 (m, 1 H) 6.51 (d, $J=7.6$ Hz, 1 H) 6.86 (t, $J=6.9$ Hz, 1 H) 6.94 (d, $J=7.6$ Hz, 1 H) 7.07 (dd, $J=7.7$, 4.6 Hz, 2 H) 7.12 - 7.20 (m, 2 H) 7.32 (t, $J=7.9$ Hz, 1 H)

5 LC/MS (method LC-C): R_t 2.80 min, MH^+ 442

$[\alpha]_D^{20}$: -327.83° (c 0.212, DMF)

Chiral HPLC (method HPLC-B): R_t 7.10 min, chiral purity 100%.

10 **Example 34:** synthesis of (18 $^*R$)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2- b :4',3'- k][1,2,5]triazacyclotridecine-11,13-dione (Compound **34A**) and (18 $^*S$)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2- b :4',3'- k][1,2,5]triazacyclotridecine-11,13-dione (Compound **34B**)



Synthesis of intermediate 34a:

(4-(but-3-en-1-yl)pyridin-3-yl)(phenyl)methanol (intermediate **34a**, 0.86 g) was obtained using the procedure described for intermediate **23a** starting from 3-bromo-4-(but-3-en-1-yl)pyridine [CAS 1309650-03-0].

5

Synthesis of intermediate 34b:

4-(but-3-en-1-yl)-3-(chloro(phenyl)methyl)pyridine (intermediate **34b**, 0.9 g) was obtained using the procedure described for intermediate **11c**.

10 **Synthesis of intermediate 34c:**

3-allyl-5-(benzyloxy)-1-((4-(but-3-en-1-yl)pyridin-3-yl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **34c**, 0.95 g) was obtained using the procedure described for intermediate **5e**.

15 **Synthesis of intermediate 34d:**

(*Z)-12-(benzyloxy)-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (intermediate **34d**, 0.44 g) was obtained using the procedure described for intermediate **5f**.

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralpak® AD-H 5 µm 250 x 30 mm, Mobile phase: 70% CO₂, 30% MeOH) to give the first eluted enantiomer **34dA** (142 mg) and the second eluted enantiomer **34dB** (145 mg).

Synthesis of Compound 34A:

(18*R)-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **34A**, 18 mg) was obtained using the procedure described for compound **8**.

25

Compound 34A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.66 (q, *J*=12.4 Hz, 1 H) 1.24 - 1.36 (m, 1 H) 1.36 - 1.53 (m, 2 H) 1.58 - 1.73 (m, 1 H) 1.89 - 2.04 (m, 1 H) 2.52 - 2.68 (m, 3 H) 3.93 (br t, *J*=12.6 Hz, 1 H) 4.36 (d, *J*=13.9 Hz, 1 H) 5.02 (br d, *J*=13.9 Hz, 1 H) 5.42 (br d, *J*=7.6 Hz, 1 H) 5.58 (s, 1 H) 7.00 (br d, *J*=7.6 Hz, 1 H) 7.16 - 7.44 (m, 6 H) 8.42 (d, *J*=5.0 Hz, 1 H) 9.13 (s, 1 H) 11.37 (br s, 1 H)

LC/MS (method LC-C): R_t 2.18 min, MH⁺ 417

35 [α]_D²⁰: -342.02° (c 0.119, DMF)

Synthesis of Compound 34B:

(18^{*S})-12-hydroxy-18-phenyl-5,6,7,8,9,18-hexahydro-10,17-methanodipyrido[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **34B**, 18 mg) was obtained using the procedure described for compound **8**.

5

Compound 34B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.57 - 0.73 (m, 1 H) 1.23 - 1.58 (m, 3 H) 1.58 - 1.72 (m, 1 H) 1.90 - 2.04 (m, 1 H) 2.47 - 2.53 (m, 2 H) 2.60 - 2.75 (m, 1 H) 3.93 (br t, *J*=12.6 Hz, 1 H) 4.36 (d, *J*=13.9 Hz, 1 H) 5.02 (br d, *J*=13.9 Hz, 1 H) 5.42 (br d, *J*=7.6 Hz, 1 H) 5.58 (s, 1 H) 7.00 (br d, *J*=7.6 Hz, 1 H) 7.07 - 7.56 (m, 6 H) 8.42 (d, *J*=5.0 Hz, 1 H) 9.13 (s, 1 H) 11.29 (br s, 1 H)

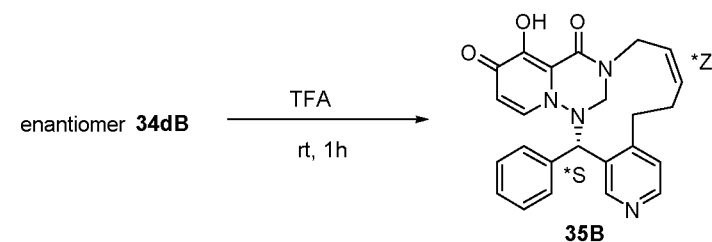
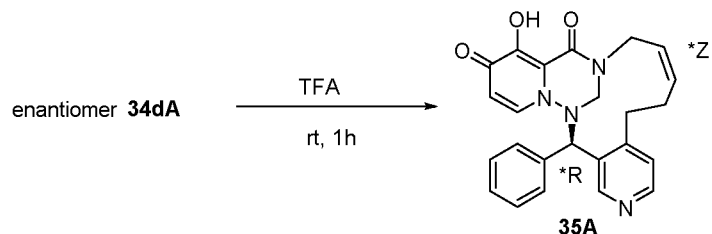
10

LC/MS (method LC-C): *R*_t 2.18 min, *MH*⁺ 417

[α]_D²⁰: +342.28° (c 0.149, DMF)

15

Example 35: synthesis of (18^{*R},^{*Z})-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **35A**) and (18^{*S},^{*Z})-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **35B**)



20

Synthesis of Compound 35A:

(18^{*R},^{*Z})-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **35A**, 77 mg) was obtained using the procedure described for compound **5A**.

25

Compound 35A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.85 - 2.18 (m, 1 H) 2.54 - 2.72 (m, 3 H) 2.95 - 3.17 (m, 1 H) 4.34 (d, *J* = 14.2 Hz, 1 H) 4.71 (br dd, *J* = 14.2, 5.1 Hz, 1 H) 5.14 (d, *J* = 13.6 Hz, 1 H) 5.25 (s, 1 H) 5.45 (d, *J* = 7.6 Hz, 1 H) 5.48 - 5.71 (m, 1 H) 5.81 - 6.18 (m, 1 H) 6.92 - 7.47 (m, 7 H) 8.50 (d, *J* = 4.6 Hz, 1 H) 9.28 (s, 1 H)

LC/MS (method LC-C): R_t 2.10 min, MH⁺ 415

[α]_D²⁰: -592.86° (c 0.140, DMF)

Chiral HPLC (method HPLC-A): R_t 4.58 min, chiral purity 100%.

10 Synthesis of Compound 35B:

(18**S*,**Z*)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrdo[1,2-*b*:4',3'-*k*][1,2,5]triazacyclotridecine-11,13-dione (Compound **35B**, 71 mg) was obtained using the procedure described for compound **5A**.

15 Compound 35B:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.96 - 2.20 (m, 1 H) 2.53 - 2.69 (m, 3 H) 2.94 - 3.20 (m, 1 H) 4.34 (d, *J* = 13.6 Hz, 1 H) 4.71 (br dd, *J* = 13.6, 5.1 Hz, 1 H) 5.14 (d, *J* = 13.6 Hz, 1 H) 5.25 (s, 1 H) 5.45 (d, *J* = 7.6 Hz, 1 H) 5.51 - 5.65 (m, 1 H) 5.96 (dt, *J* = 15.4, 7.5 Hz, 1 H) 7.13 - 7.33 (m, 7 H) 8.50 (d, *J* = 4.6 Hz, 1 H) 9.28 (s, 1 H)

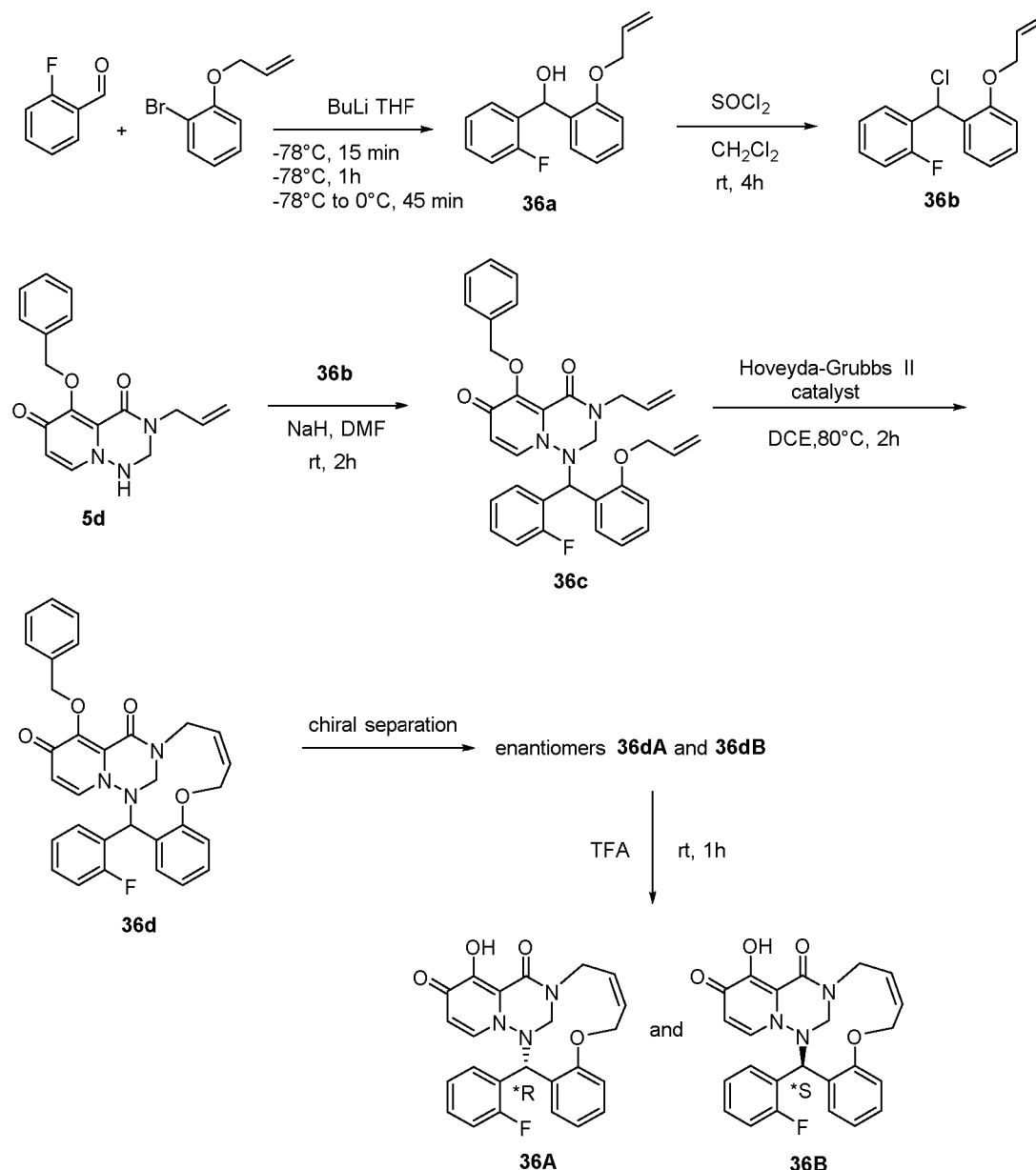
20 LC/MS (method LC-C): R_t 2.10 min, MH⁺ 415

[α]_D²⁰: +600° (c 0.112, DMF)

Chiral HPLC (method HPLC-A): R_t 6.07 min, chiral purity 100%.

Example 36: synthesis of (18**R*,*Z*)-18-(2-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **36A**) and (18**S*,*Z*)-18-(2-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **36B**)

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Synthesis of intermediate **36a**:

Under N₂ flow at -78°C, *n*-BuLi (1.6 M in hexane) (9.7 mL, 15.49 mmol) was added dropwise to a solution of 1-(allyloxy)-2-bromobenzene [CAS 60333-75-7] (3.0 g, 14.08 mmol) in dry THF (25 mL). The mixture was stirred 15 min at this temperature then 2-fluorobenzaldehyde [CAS 446-52-6] (1.78 mL, 16.90 mmol) was added dropwise. The mixture was stirred at -78°C for 1 h, and then slowly warmed up to 0°C over 45 min. The reaction was quenched with NH₄Cl 10% aqueous solution and the aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in EtOH (50 mL) and SiliaMetS[®] diamine (1.8 g, 2.816 mmol) was added. The mixture was stirred at rt for 4 h and then filtered. The filtrate was concentrated under reduced pressure.

Purification was carried out by flash chromatography over silica gel (15-40 μm , 80 g, heptane/EtOAc from 95/5 to 80/20). The pure fractions were collected and concentrated to dryness to give (2-(allyloxy)phenyl)(2-fluorophenyl)methanol (intermediate **36a**, 2 g).

5 **Synthesis of intermediate 36d:**

(Z)-12-(benzyloxy)-18-(2-fluorophenyl)-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **36d**, 460 mg) was obtained using the procedures described in example 5 starting from intermediates **36b** (synthesized as **5a**) and **5d**.

- 10 The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel[®] OD-H 5 μm 250 x 30 mm, Mobile phase: 60% CO₂, 40% EtOH) to give the first eluted enantiomer **36dA** (195 mg) and the second eluted enantiomer **36dB** (195 mg).

Synthesis of Compound 36A:

- 15 (18**R,Z*)-18-(2-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **36A**, 62 mg) was obtained using the procedure described for compound **5A**.

Compound 36A:

- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.22 (br dd, *J*=13.9, 8.5 Hz, 1 H) 4.23 (br d, *J*=13.9 Hz, 1 H) 4.33 (br s, 1 H) 4.70 - 4.84 (m, 2 H) 5.12 (d, *J*=13.9 Hz, 1 H) 5.53 (d, *J*=7.6 Hz, 1 H) 5.88 (br s, 1 H) 5.97 (br s, 1 H) 6.03 - 6.14 (m, 1 H) 6.99 (br t, *J*=9.3 Hz, 1 H) 7.09 (br t, *J*=7.4 Hz, 1 H) 7.15 - 7.33 (m, 3 H) 7.34 - 7.39 (m, 1 H) 7.44 (q, *J*=8.0 Hz, 2 H) 8.12 (br d, *J*=7.3 Hz, 1 H) 10.47 - 11.36 (m, 1 H)
- 25 LC/MS (method LC-C): *R*_t 2.48 min, *MH*⁺ 434
[α]_D²⁰: -672.67° (c 0.3, DMF)
Chiral HPLC (method HPLC-A): *R*_t 5.04 min, chiral purity 100%.

Synthesis of Compound 36B:

- 30 (18**S,Z*)-18-(2-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **36B**, 95 mg) was obtained using the procedure described for compound **5A**.

Compound 36B:

- 35 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.22 (br dd, *J*=13.9, 8.5 Hz, 1 H) 4.23 (d, *J*=13.6 Hz, 1 H) 4.33 (br s, 1 H) 4.69 - 4.86 (m, 2 H) 5.12 (d, *J*=13.9 Hz, 1 H) 5.53 (d, *J*=7.6 Hz, 1 H) 5.88 (br s, 1 H) 5.97 (br s, 1 H) 6.08 (dt, *J*=15.1, 7.3 Hz, 1 H) 6.99 (t, *J*=9.1 Hz, 1

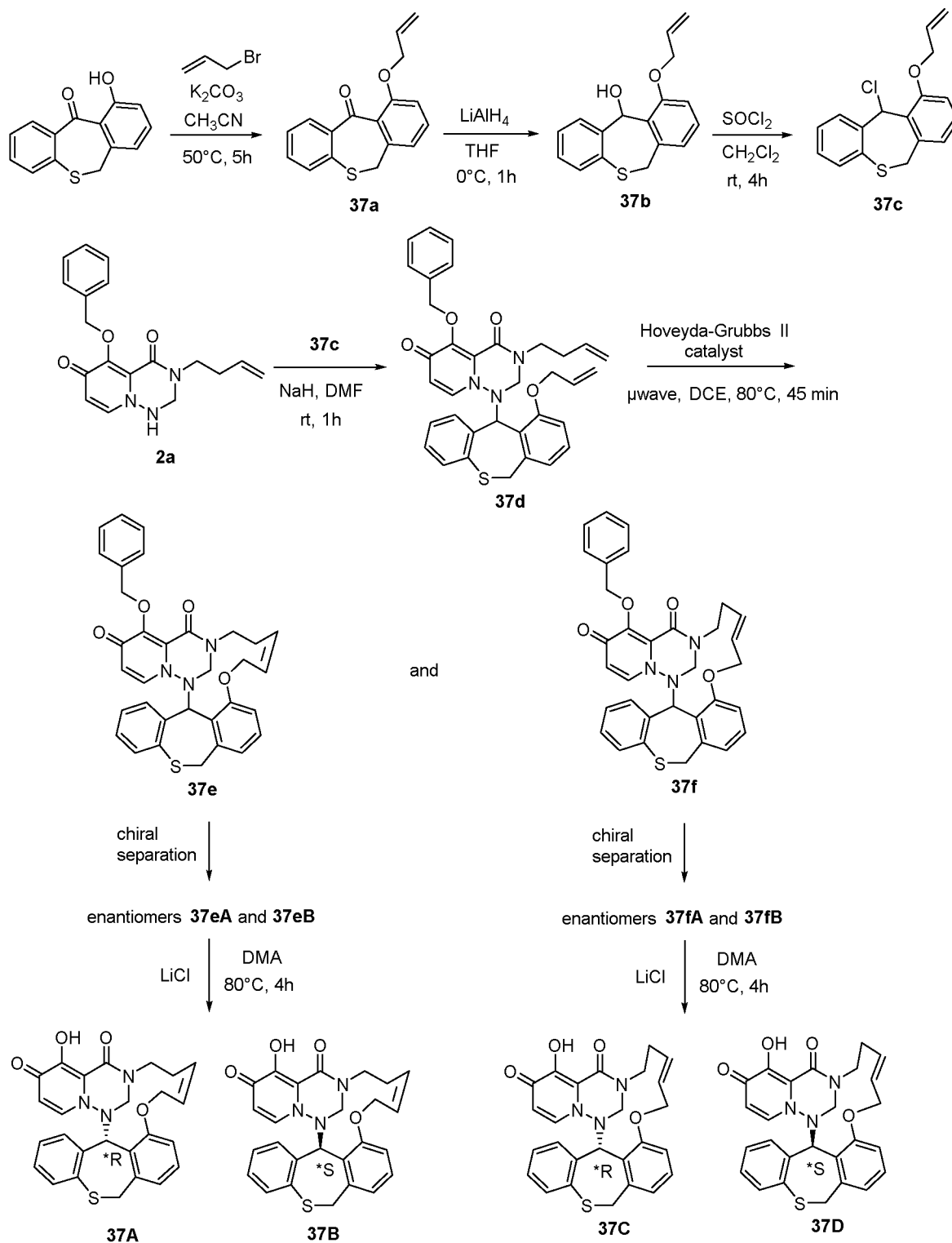
H) 7.09 (t, $J=7.6$ Hz, 1 H) 7.20 - 7.32 (m, 3 H) 7.33 - 7.39 (m, 1 H) 7.44 (q, $J=8.0$ Hz, 2 H) 8.12 (br d, $J=7.3$ Hz, 1 H) 10.33 - 11.43 (m, 1 H)

LC/MS (method LC-C): R_t 2.48 min, MH^+ 434

$[\alpha]_D^{20}$: +606.82° (c 0.264, DMF)

5 Chiral HPLC (method HPLC-B): R_t 6.87 min, chiral purity 100%.

Example 37: synthesis of (1*R,13Z)-7-hydroxy-16-oxa-23-thia-2,3,10-triazahehexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione (Compound **37A**), (1*S,13Z)-7-hydroxy-16-oxa-23-thia-2,3,10-triazahehexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione (Compound **37B**), (1*R,13E)-7-hydroxy-16-oxa-23-thia-2,3,10-triazahehexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaen-9-one (Compound **37C**) and (1*S,13E)-7-hydroxy-16-oxa-23-thia-2,3,10-triazahehexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione(Compound **37D**)



Synthesis of intermediate 37a:

A mixture of 10-hydroxydibenzo[*b,e*]thiepin-11(6*H*)-one [CAS 1370250-54-6] (10.8 g, 44.57 mmol), allyl bromide [CAS 106-95-6] (6.7 mL, 46.80 mmol) and K_2CO_3 (18.5 g, 133.72 mmol) in CH_3CN (150 mL) was stirred at 50°C for 5 h. The mixture was cooled down to rt and concentrated under reduced pressure. The residue was taken up with

EtOAc and water. The two layers were separated. The organic phase was washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to give 10-(allyloxy)dibenzo[*b,e*]thiepin-11(6*H*)-one (intermediate **37a**, 12 g).

5 Synthesis of intermediate 37b:

At 0°C under N₂, LiAlH₄ (1M in THF) (51 mL, 51.0 mmol) was added dropwise to a solution of 10-(allyloxy)dibenzo[*b,e*]thiepin-11(6*H*)-one (intermediate **37a** 12.0 g, 42.49 mmol) in THF (200 mL). The mixture was stirred at 0°C for 1 h, diluted with EtOAc, and then quenched by the dropwise addition of water. The mixture was filtered through
10 celite[®]. The two layers were decanted. The organic layer was washed with water and brine, dried over MgSO₄, filtered and the solvent was concentrated under reduced pressure to give 10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (intermediate **37b**, 12.2 g). The compound was used as such in the next step.

15 Synthesis of intermediate 37c:

At 0°C, SOCl₂ (1.5 mL, 2.28 mmol) was added dropwise to a solution of 10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (intermediate **37b**, 4.8 g, 16.88 mmol) in CH₂Cl₂ (86 mL). The mixture was stirred at 0°C for 30 min, then at rt for 4 h. The solution was concentrated to dryness. The residue was taken up with toluene and concentrated again
20 to give 10-(allyloxy)-11-chloro-6,11-dihydrodibenzo[*b,e*]thiepine (intermediate **37c**, 5.11 g), which was used as such in the next step.

Synthesis of intermediate 37d:

Under N₂ and at 0°C, NaH (60% dispersion in mineral oil) (1.23 g, 30.75 mmol) was
25 added to a solution of 5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **2a**, 6.67 g, 20.50 mmol) in DMF (100 mL). The mixture was stirred for 30 min at 0°C. 10-(allyloxy)-11-chloro-6,11-dihydrodibenzo[*b,e*]thiepine (intermediate **37c**, 7.45 g, 24.60 mmol) in DMF (50 mL) was added dropwise and the mixture was stirred at rt for 1 h. The mixture was poured in
30 water/ice (500 mL). The precipitate was filtered off and washed with water. The precipitate was taken up with CH₂Cl₂, dried over MgSO₄, filtered and the solvent was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (20-45 µm, 120 g, CH₂Cl₂/CH₃OH from 99/1 to 96/4. The pure fractions were collected and concentrated to dryness to give a first batch of 1-
35 (10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **37d**, 8.75 g). Other fractions containing the desired product were combined (2 g) and a second purification was carried out by flash chromatography over silica gel (15-40 µm, 80g,

CH₂Cl₂/EtOAc from 85/15 to 75/25). The pure fractions were collected and concentrated to dryness to give a second batch of intermediate **37d** (1.15 g).

Synthesis of intermediates **37e** and **37f**:

5 The reaction was performed in an Anton-Paar microwave oven on two batches in parallel. A degassed solution of 1-(10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **37d**, 2x4.1 g, 13.86 mmol) and Hoveyda-Grubbs catalyst 2nd generation [CAS 301224-40-8] (2x0.87 g, 2.77 mmol) in dry DCE (2x500 mL) was stirred at 80°C
10 for 25 min. The mixture was cooled down to rt and SiliaMetS[®] DMT (2x9 g, 11.09 mmol) was added and the mixture was stirred at rt for 4 h. The reaction mixture was filtered through celite[®], the celite[®] was washed with CH₂Cl₂ and the filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 µm, 330 g, CH₂Cl₂/CH₃OH from 99.5/0.5 to 96/4)). A second purification was
15 performed by flash chromatography over silica gel (15 µm, 120 g, Toluene/*i*PrOH 92/8), and then two other purifications were carried out by flash chromatography over silica gel (15 µm, 120 g, Toluene/*i*PrOH 93/7) to give intermediate **37e** (1.23 g, *Z* isomer) and intermediate **37f** (320 mg, *E* isomer).

The two enantiomers of intermediate **37e** were separated via chiral SFC (Stationary phase: Whelk-O1 (*S,S*) 5 µm 250 x 21.2 mm, Mobile phase: 45% CO₂, 55% EtOH+10% CH₂Cl₂) to give the first eluted enantiomer **37eA** (530 mg) and the second eluted enantiomer **37eB** (520 mg).

The two enantiomers of intermediate **37f** were separated via chiral SFC (Stationary phase: Whelk-O1 (*S,S*) 5 µm 250 x 21.2 mm, Mobile phase: 45% CO₂, 55% EtOH+10% CH₂Cl₂) to give the first eluted enantiomer **37fA** (134 mg) and the second eluted enantiomer **37fB** (133 mg).

Synthesis of Compound **37A**:

LiCl (199 mg, 4.70 mmol) was added to a solution of enantiomer **37eA** (530 mg, 0.94 mmol) in DMA (5 mL) and the mixture was stirred at 80°C for 4 h. The mixture was cooled down to rt and a mixture of ice and an aqueous solution of HCl 0.5 N was added. The aqueous layer was extracted with CH₂Cl₂. The organic phase was washed 3 times with an aqueous solution of HCl 0.5 N, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica
35 gel (15-40 µm, 12 g, CH₂Cl₂/CH₃OH from 99/1 to 97/3). The pure fractions were collected and concentrated to dryness to give after freeze-drying from water/CH₃CN (8/2) compound **37A** (187 mg).

Compound 37A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.11 - 2.31 (m, 2 H) 2.85 (br d, *J*=14.2 Hz, 1 H) 3.82 (d, *J*=13.2 Hz, 1 H) 4.19 - 4.33 (m, 2 H) 4.52 (d, *J*=6.9 Hz, 2 H) 4.95 (d, *J*=13.2 Hz, 1 H) 5.56 (d, *J*=7.9 Hz, 1 H) 5.71 (d, *J*=13.2 Hz, 1 H) 5.97 (td, *J*=10.6, 3.9 Hz, 1 H) 6.04 - 6.15 (m, 2 H) 6.58 (d, *J*=7.3 Hz, 1 H) 6.78 - 6.85 (m, 1 H) 7.05 (d, *J*=8.2 Hz, 3 H) 7.08 - 7.14 (m, 1 H) 7.24 (d, *J*=7.6 Hz, 1 H) 7.37 (t, *J*=7.9 Hz, 1 H) 11.52 - 11.97 (m, 1 H)

LC/MS (method LC-C): *R*_t 2.76 min, MH⁺ 474

[α]_D²⁰: +189.43° (c 0.331, DMF)

Chiral HPLC (method HPLC-B): *R*_t 6.36 min, chiral purity 100%.

Synthesis of Compound 37B:

LiCl (194 mg, 4.57 mmol) was added to a solution of enantiomer **37eB** (515 mg, 0.91 mmol) in DMA (5 mL) and the mixture was stirred at 80°C for 4 h. The mixture was cooled down to rt and a mixture of ice and an aqueous solution of HCl 0.5 N was added. The aqueous layer was extracted with CH₂Cl₂. The organic phase was washed 3 times with an aqueous solution of HCl 0.5 N, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (15-40 μm, 12 g, CH₂Cl₂/CH₃OH from 99/1 to 97/3). The pure fractions were collected and concentrated to dryness to give after freeze-drying from water/CH₃CN (8/2) compound **37B** (255 mg).

Compound 37B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.12 - 2.31 (m, 2 H) 2.85 (br d, *J*=14.2 Hz, 1 H) 3.82 (d, *J*=13.2 Hz, 1 H) 4.20 - 4.35 (m, 2 H) 4.52 (d, *J*=7.3 Hz, 2 H) 4.95 (d, *J*=13.2 Hz, 1 H) 5.56 (d, *J*=7.6 Hz, 1 H) 5.71 (d, *J*=13.2 Hz, 1 H) 5.92 - 6.01 (m, 1 H) 6.04 - 6.13 (m, 2 H) 6.58 (d, *J*=6.9 Hz, 1 H) 6.81 (td, *J*=7.4, 1.3 Hz, 1 H) 7.05 (d, *J*=8.5 Hz, 3 H) 7.08 - 7.14 (m, 1 H) 7.24 (d, *J*=7.6 Hz, 1 H) 7.37 (t, *J*=7.9 Hz, 1 H) 11.56 - 11.91 (m, 1 H)

LC/MS (method LC-C): *R*_t 2.76 min, MH⁺ 474

[α]_D²⁰: -184.01° (c 0.344, DMF)

Chiral HPLC (method HPLC-B): *R*_t 9.80 min, chiral purity 100%.

Synthesis of Compound 37C:

Compound **37C** (67 mg) was obtained using the procedure described for compound **37A**.

Compound 37C:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.15 - 2.23 (m, 1 H) 2.76 - 2.85 (m, 2 H) 3.74 - 3.82 (m, 1 H) 3.85 (d, *J*=13.2 Hz, 1 H) 4.16 (d, *J*=12.9 Hz, 1 H) 4.43 - 4.51 (m, 1 H) 4.74

(dd, $J=11.7, 5.4$ Hz, 1 H) 5.01 (d, $J=12.9$ Hz, 1 H) 5.50 - 5.60 (m, 2 H) 5.67 (d, $J=13.2$ Hz, 1 H) 5.86 (s, 1 H) 5.92 (ddd, $J=15.1, 9.7, 5.5$ Hz, 1 H) 6.80 - 6.90 (m, 2 H) 7.01 - 7.07 (m, 1 H) 7.08 - 7.16 (m, 2 H) 7.18 - 7.27 (m, 2 H) 7.37 (t, $J=7.9$ Hz, 1 H) 11.94 (br s, 1 H)

5 LC/MS (method LC-C): R_t 2.73 min, MH^+ 474

$[\alpha]_D^{20}$: +280.56° (c 0.252, DMF)

Chiral HPLC (method HPLC-B): R_t 6.34 min, chiral purity 100%.

Synthesis of Compound 37D:

10 Compound 37D (67 mg) was obtained using the procedure described for compound 37A.

Compound 37D:

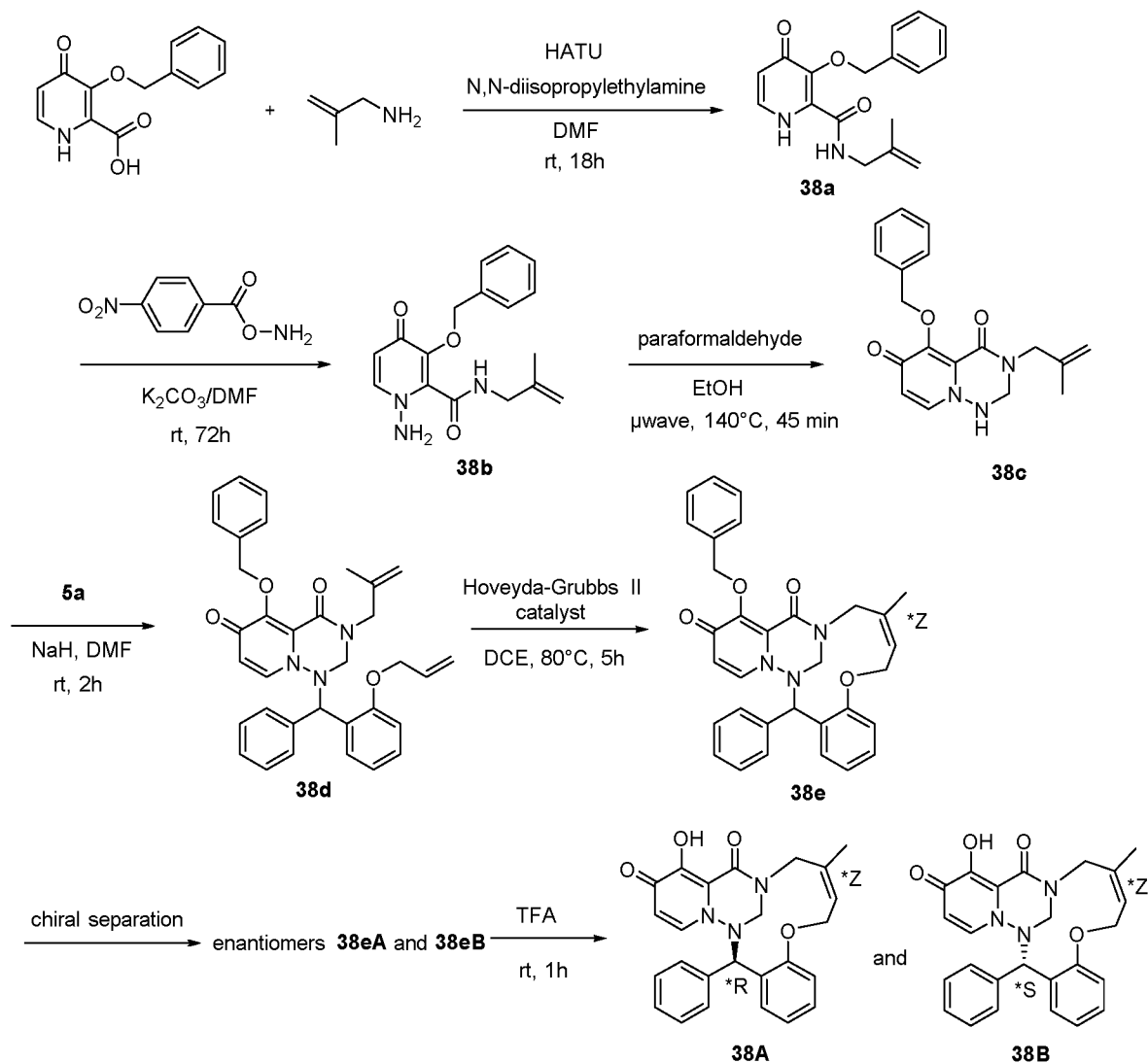
^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.13 - 2.25 (m, 1 H) 2.75 - 2.90 (m, 2 H) 3.72 - 3.82 (m, 1 H) 3.85 (br d, $J=13.2$ Hz, 1 H) 4.15 (br d, $J=12.9$ Hz, 1 H) 4.47 (br t, $J=10.9$ Hz, 1 H) 4.74 (br dd, $J=11.7, 5.4$ Hz, 1 H) 5.00 (br d, $J=12.9$ Hz, 1 H) 5.49 - 5.60 (m, 2 H) 5.67 (br d, $J=13.2$ Hz, 1 H) 5.86 (s, 1 H) 5.92 (ddd, $J=15.2, 9.5, 5.2$ Hz, 1 H) 6.78 - 6.90 (m, 2 H) 7.00 - 7.07 (m, 1 H) 7.07 - 7.16 (m, 2 H) 7.22 (dd, $J=16.9, 8.0$ Hz, 2 H) 7.37 (t, $J=7.7$ Hz, 1 H) 11.91 (br s, 1 H)

LC/MS (method LC-C): R_t 2.73 min, MH^+ 474

20 $[\alpha]_D^{20}$: -280.56° (c 0.324, DMF)

Chiral HPLC (method HPLC-B): R_t 8.17 min, chiral purity 99.25%.

Example 38: synthesis of (18 $^*R,Z$)-12-hydroxy-8-methyl-18-phenyl-6,9-dihydro-18 H -10,17-methanobenzo[b]pyrido[1,2- f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound 38A) and (18 $^*S,Z$)-12-hydroxy-8-methyl-18-phenyl-6,9-dihydro-18 H -10,17-methanobenzo[b]pyrido[1,2- f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound 38B)



Synthesis of intermediate **38a**:

3-(benzyloxy)-*N*-(2-methylallyl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **38a**, 4.4 g) was obtained using the procedure described for intermediate **5b** starting from 2-methylprop-2-en-1-amine [CAS 2878-14-0].

Synthesis of intermediate **38b**:

1-amino-3-(benzyloxy)-*N*-(2-methylallyl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **38b**, 2.7 g) was obtained using the procedure described for intermediate **5c**.

Synthesis of intermediate **38c**:

5-(benzyloxy)-3-(2-methylallyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **38c**, 1.8 g) was obtained using the procedure described for intermediate **5d**.

Synthesis of intermediate 38d:

1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(2-methylallyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **38d**, 1.2 g) was obtained using the procedure described for intermediate **5e**.

5

Synthesis of intermediate 38e:

(*Z)-12-(benzyloxy)-8-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **38e**, 420 mg) was obtained using the procedure described for intermediate **5f**.

10

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralpak® AS-H 5 µm 250 x 20 mm, Mobile phase: 45% CO₂, 55% EtOH) to give the first eluted enantiomer **38eA** (134 mg) and the second eluted enantiomer **38eB** (145 mg).

Synthesis of Compound 38A:

(18*R,*Z)-12-hydroxy-8-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **38A**, 80 mg) was obtained using the procedure described for compound **5A**.

Compound 38A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.57 (br s, 3 H) 3.09 (d, *J*=14.2 Hz, 1 H) 4.16 (d, *J*=13.6 Hz, 1 H) 4.40 - 4.59 (m, 1 H) 4.68 - 4.83 (m, 1 H) 4.88 (d, *J*=14.2 Hz, 1 H) 5.12 (d, *J*=13.1 Hz, 1 H) 5.34 (s, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.85 (br t, *J*=7.8 Hz, 1 H) 6.94 - 7.51 (m, 9 H) 8.08 (br d, *J*=7.1 Hz, 1 H)

LC/MS (method LC-C): R_t 2.62 min, MH⁺ 430

[α]_D²⁰: +657.75° (c 0.213, DMF)

Chiral HPLC (method HPLC-B): R_t 5.57 min, chiral purity 100%.

Synthesis of Compound 38B:

(18*S,*Z)-12-hydroxy-8-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **38B**, 80 mg) was obtained using the procedure described for compound **5A**.

Compound 38B:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.56 (br s, 3 H) 3.09 (d, *J*=14.2 Hz, 1 H) 4.16 (d, *J*=13.6 Hz, 1 H) 4.51 (dd, *J*=11.6, 9.1 Hz, 1 H) 4.77 (dd, *J*=12.1, 7.1 Hz, 1 H) 4.89 (br d, *J*=14.2 Hz, 1 H) 5.12 (d, *J*=13.6 Hz, 1 H) 5.34 (s, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.85 (br t, *J*=7.8 Hz, 1 H) 7.11 - 7.28 (m, 7 H) 7.31 - 7.42 (m, 2 H) 8.07 (br d, *J*=7.6 Hz, 1 H)

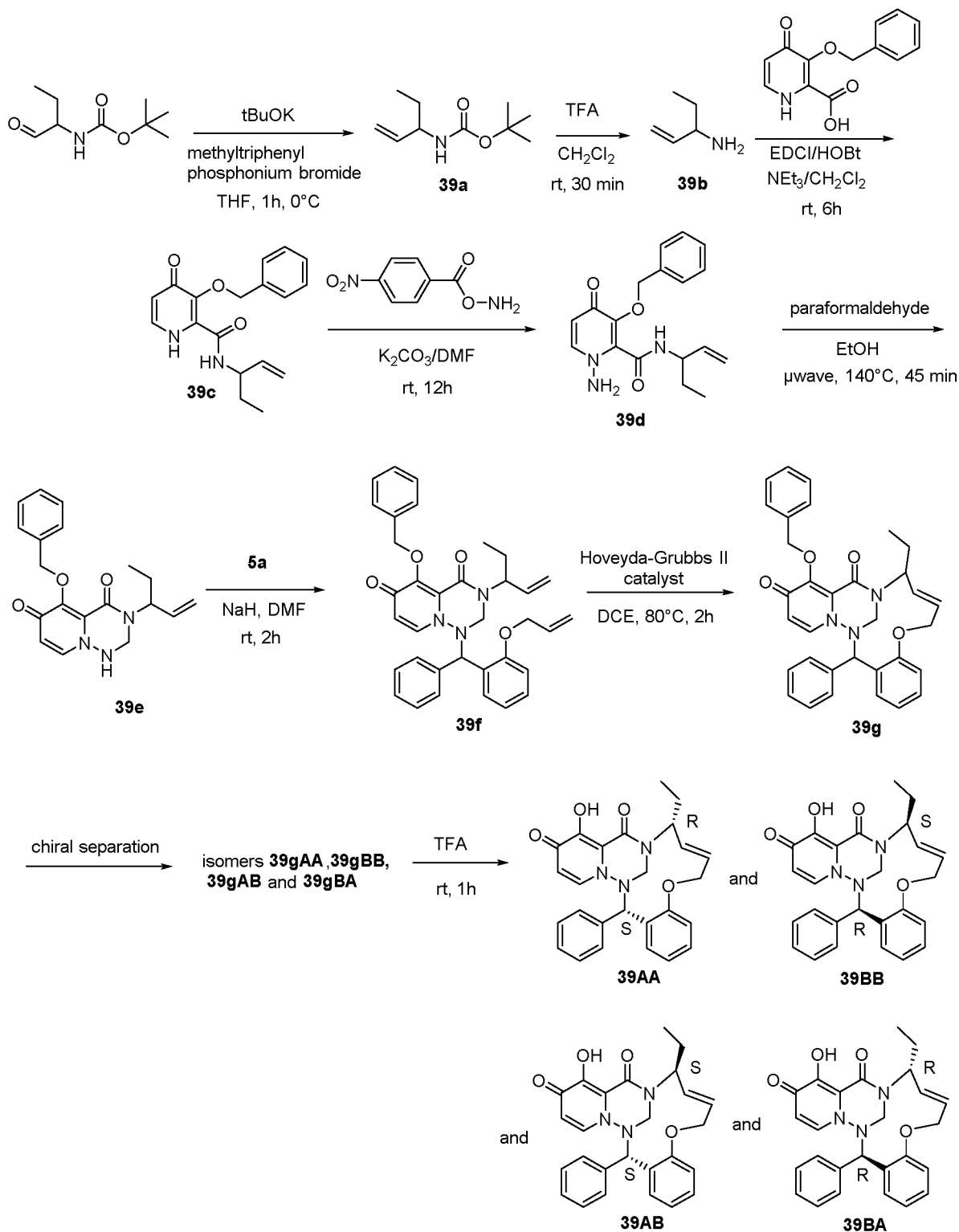
35

LC/MS (method LC-C): R_t 2.62 min, MH^+ 430

$[\alpha]_D^{20}$: -687.4° (c 0.246, DMF)

Chiral HPLC (method HPLC-B): R_t 7.04 min, chiral purity 100%.

- 5 Example 39: synthesis of (9R,18S,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **39AA**) and (9S,18R,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **39BB**) and (9S,18S,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **39AB**) and (9R,18R,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **39BA**)
- 10



Synthesis of intermediate 39a:

To a suspension of methyltriphenylphosphonium bromide [CAS 1779-49-3] (36.0 g, 100.94 mmol) in THF (300 mL) at 0°C was added $t\text{BuOK}$ (9.7 g, 86.52 mmol) portionwise. The resulting bright yellow suspension was stirred at 0°C for 30 min. A solution of *tert*-butyl (1-oxobutan-2-yl)carbamate [CAS 346690-97-9] (13.5 g, 72.10

mmol) in THF (100 mL) was then added dropwise. The resulting pale-yellow mixture was stirred for 1 h at 0°C, and the reaction was quenched by the addition of acetone (50 mL). The suspension was diluted with hexane, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc from 100:0 to 90:10) to give *tert*-butyl pent-1-en-3-ylcarbamate (intermediate **39a**, 6.5 g).

Synthesis of intermediate 39b:

A solution of *tert*-butyl pent-1-en-3-ylcarbamate (intermediate **39a**, 6.5 g, 35.09 mmol) in CH₂Cl₂/TFA (1:1) (60 mL) was stirred at rt for 30 min. The solution was concentrated under reduced pressure and co-evaporated twice with toluene. The residue was purified by flash chromatography over silica gel (CH₂Cl₂/MeOH from 100:0 to 80:20) to give pent-1-en-3-amine (intermediate **39b**, 2.8 g).

Synthesis of intermediate 39c:

3-(benzyloxy)-4-oxo-N-(pent-1-en-3-yl)-1,4-dihydropyridine-2-carboxamide (intermediate **39c**, 6.1 g) was obtained using the procedure described for intermediate **1a**.

Synthesis of intermediate 39d:

1-amino-3-(benzyloxy)-4-oxo-N-(pent-1-en-3-yl)-1,4-dihydropyridine-2-carboxamide (intermediate **39d**, 3.5 g) was obtained using the procedure described for intermediate **5c**.

Synthesis of intermediate 39e:

5-(benzyloxy)-3-(pent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **39e**, 830 mg) was obtained using the procedure described for intermediate **5d**.

Synthesis of intermediate 39f:

1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(pent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **39f**, 980 mg) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 39g:

A degassed solution of 1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(pent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **39f**, 1.0 g, 1.78 mmol) and Hoveyda-Grubbs catalyst 2nd generation [CAS 301224-40-8] (223 mg,

0.36 mmol) in dry DCE (135 mL) was stirred at 80°C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (120 g, CH₂Cl₂/MeOH from 100:0 to 98:2). The compound was purified again by flash chromatography over silica gel (petroleum ether/EtOAc from 100:0 to 0:100) and by reverse phase chromatography (C18: 40 µm, 45 g, H₂O/MeOH from 70:30 to 0:100) to give (*E*)-12-(benzyloxy)-9-ethyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **39g**, 580 mg).

The 4 isomers (780 mg batch) were separated. A first separation via achiral SFC (Stationary phase: diethylaminopropyl 5 µm 150 x 30 mm, Mobile phase: 90% CO₂, 10% MeOH) delivered fraction 1 (460 mg) and fraction 2 (196 mg). Isomers of fraction 1 were separated via chiral SFC (Stationary phase: Chiralpak[®] IC 5 µm 250 x 30mm, Mobile phase: 40% CO₂, 60% MeOH) to give isomer **39gAA** (203 mg) and isomer **39gBB** (217 mg). Isomers of fraction 2 were separated via chiral SFC (Stationary phase: Chiralpak[®] IC 5 µm 250 x 21.2 mm, Mobile phase: 40% CO₂, 60% MeOH) to give isomer **39gAB** (48 mg) and fraction 3 (65 mg). Fraction 3 was purified by chiral SFC (Stationary phase: Chiralpak[®] IA 5 µm 250 x 20 mm, Mobile phase: 70% CO₂, 30% EtOH) to give isomer **39gBA** (35 mg).

Synthesis of Compound **39AA**:

(9*R*,18*S*,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **39AA**, 95 mg) was obtained using the procedure described for compound **5A**.

Compound **39AA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.81 (t, *J*=7.4 Hz, 3 H) 1.36 - 1.56 (m, 2 H) 4.09 (t, *J*=10.9 Hz, 1 H) 4.19 (d, *J*=13.6 Hz, 1 H) 4.87 (dd, *J*=11.3, 5.7 Hz, 1 H) 5.03 (d, *J*=13.6 Hz, 1 H) 5.16 (q, *J*=7.3 Hz, 1 H) 5.22 (s, 1 H) 5.35 (br dd, *J*=15.8, 6.6 Hz, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 6.30 (ddd, *J*=15.8, 10.1, 5.7 Hz, 1 H) 7.10 - 7.26 (m, 7 H) 7.33 - 7.39 (m, 1 H) 7.40 - 7.47 (m, 1 H) 8.08 (dd, *J*=7.7, 1.4 Hz, 1 H) 11.13 (br s, 1 H)

LC/MS (method LC-C): R_t 2.83 min, MH⁺ 444

[α]_D²⁰: +617.94° (c 0.301, DMF)

Chiral HPLC (method HPLC-B): R_t 5.64 min, chiral purity 100%.

Synthesis of Compound **39BB**:

(9*S*,18*R*,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **39BB**, 77 mg) was obtained using the procedure described for compound **5A**.

Compound 39BB:

- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.81 (t, *J*=7.3 Hz, 3 H) 1.36 - 1.56 (m, 2 H) 4.09 (t, *J*=10.7 Hz, 1 H) 4.19 (d, *J*=13.2 Hz, 1 H) 4.87 (dd, *J*=11.5, 5.5 Hz, 1 H) 5.03 (d, *J*=13.2 Hz, 1 H) 5.16 (q, *J*=7.3 Hz, 1 H) 5.22 (s, 1 H) 5.35 (br dd, *J*=15.6, 6.5 Hz, 1 H) 5.48 (d, *J*=7.9 Hz, 1 H) 6.30 (ddd, *J*=15.8, 10.1, 5.4 Hz, 1 H) 7.11 - 7.24 (m, 7 H) 7.33 - 7.39 (m, 1 H) 7.41 - 7.47 (m, 1 H) 8.08 (dd, *J*=7.7, 1.4 Hz, 1 H) 11.11 (br s, 1 H)
- 10 LC/MS (method LC-C): R_t 2.83 min, MH⁺ 444
[α]_D²⁰: -592.57° (c 0.296, DMF)
Chiral HPLC (method HPLC-B): R_t 6.66 min, chiral purity 99.06%.

Synthesis of Compound 39AB:

- 15 (9*S*,18*S*,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **39AB**, 26 mg) was obtained using the procedure described for compound **5A**.

20 **Compound 39AB:**

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.85 (t, *J*=7.4 Hz, 3 H) 2.07 - 2.18 (m, 1 H) 2.25 - 2.35 (m, 1 H) 3.39 - 3.47 (m, 1 H) 4.17 (d, *J*=13.9 Hz, 1 H) 4.50 - 4.64 (m, 2 H) 5.17 (d, *J*=13.9 Hz, 1 H) 5.46 (s, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.80 (ddd, *J*=15.1, 9.5, 5.4 Hz, 1 H) 6.38 (br dd, *J*=15.0, 9.9 Hz, 1 H) 7.02 - 7.23 (m, 5 H) 7.26 (d, *J*=7.9 Hz, 1 H) 7.30 - 7.36 (m, 2 H) 7.37 - 7.43 (m, 1 H) 8.13 (dd, *J*=7.7, 1.4 Hz, 1 H)
- 25 LC/MS (method LC-C): R_t 2.86 min, MH⁺ 444
[α]_D²⁰: +675.96° (c 0.208, DMF)
Chiral HPLC (method HPLC-A): R_t 5.00 min, chiral purity 100%.

30 **Synthesis of Compound 39BA:**

- (9*R*,18*R*,*E*)-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **39BA**, 18 mg) was obtained using the procedure described for compound **5A**.

35

Compound 39BA:

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.85 (t, *J*=7.4 Hz, 3 H) 2.06 - 2.19 (m, 1 H) 2.26 - 2.34 (m, 1 H) 3.39 - 3.48 (m, 1 H) 4.17 (d, *J*=14.2 Hz, 1 H) 4.48 - 4.66 (m, 2 H) 5.17

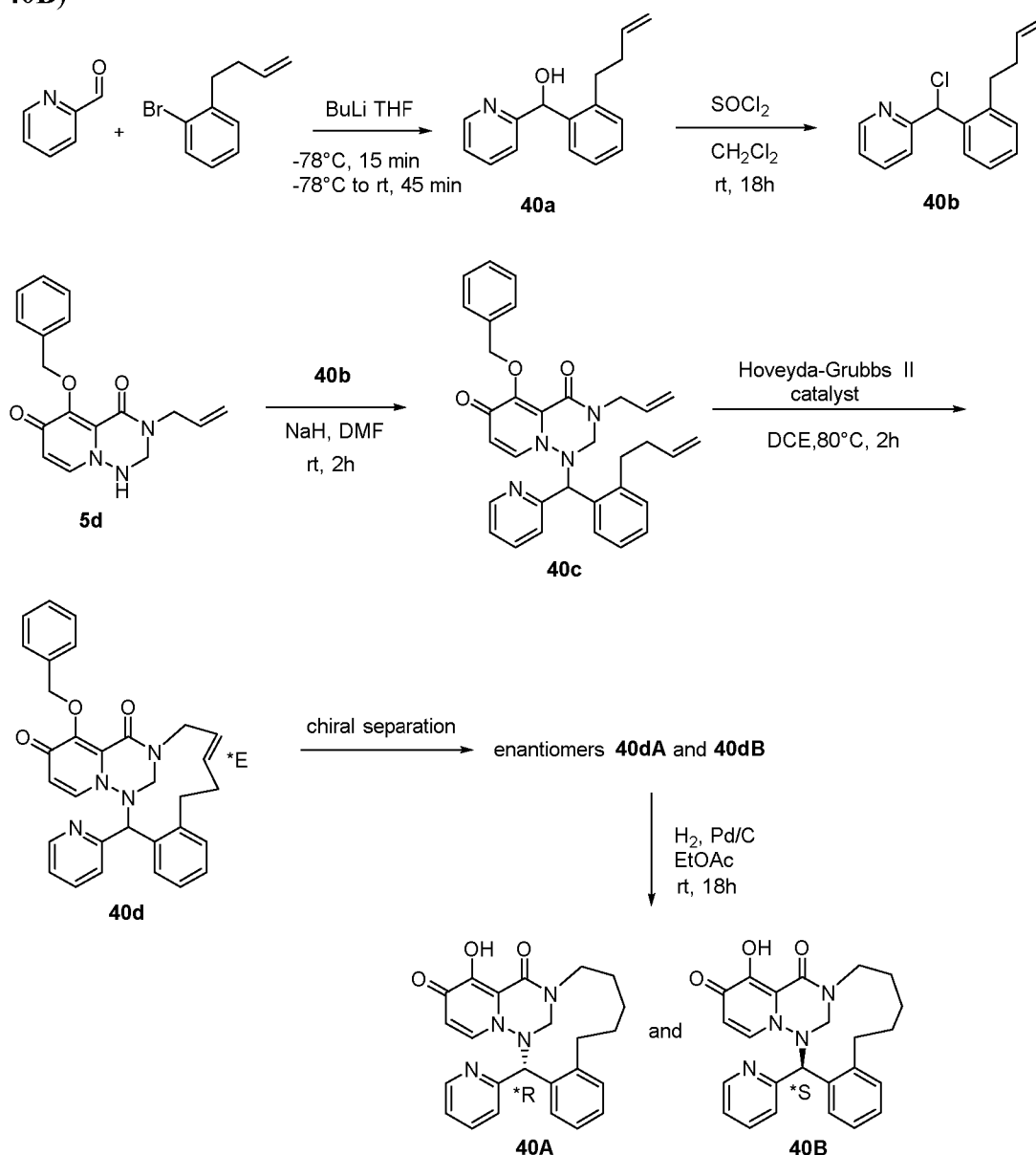
(d, $J=13.9$ Hz, 1 H) 5.46 (s, 1 H) 5.48 (d, $J=7.6$ Hz, 1 H) 5.80 (ddd, $J=15.0, 9.3, 5.4$ Hz, 1 H) 6.38 (br dd, $J=15.0, 9.9$ Hz, 1 H) 7.02 - 7.21 (m, 5 H) 7.26 (d, $J=8.2$ Hz, 1 H) 7.30 - 7.36 (m, 2 H) 7.37 - 7.44 (m, 1 H) 8.13 (dd, $J=7.6, 1.6$ Hz, 1 H)

LC/MS (method LC-C): R_t 2.86 min, MH^+ 444

5 $[\alpha]_D^{20}$: -725.74° (c 0.202, DMF)

Chiral HPLC (method HPLC-A): R_t 6.02 min, chiral purity 100%.

Example 40: synthesis of (17*R*)-4-hydroxy-16-(pyridin-2-yl)-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **40A**) and ((17*S*)-4-hydroxy-16-(pyridin-2-yl)-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **40B**)



Synthesis of intermediate 40a:

(2-(but-3-en-1-yl)phenyl)(pyridin-2-yl)methanol (intermediate **40a**, 880 mg) was obtained using the procedure described for intermediate **23a** starting from (2-(but-3-en-1-yl)phenyl)(pyridin-2-yl)methanol [CAS 1121-60-4] (9.948 mmol) and 1-bromo-2-(but-3-en-1-yl)benzene [CAS 71813-50-8] (6.63 mmol).

Synthesis of intermediate 40b:

2-((2-(but-3-en-1-yl)phenyl)chloromethyl)pyridine (intermediate **40b**, 950 mg) was obtained using the procedure described for intermediate **11c**.

Synthesis of intermediate 40c:

3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)phenyl)(pyridin-2-yl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **40c**, 920 mg) was obtained using the procedure described for intermediate **11g**.

Synthesis of intermediate 40d:

(*Z)-4-(benzyloxy)-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-b][1,2,5]triazacyclotridecine-3,5-dione (intermediate **40d**, 900 mg) was obtained using the procedure described for intermediate **5f**. The compound was used as such for the separation of the two enantiomers via chiral SFC (Stationary phase: Chiralpak[®] AD-H 5 μ m 250 x 30mm, Mobile phase: 60% CO₂, 40% MeOH) to give the first eluted enantiomer **40dA** (353 mg) and the second eluted enantiomer **40dB** (345 mg).

Synthesis of Compound 40A:

(17*R)-4-hydroxy-16-(pyridin-2-yl)-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[k]pyrido[1,2-b][1,2,5]triazacyclotridecine-3,5-dione (Compound **40A**, 79 mg) was obtained using the procedure described for compound **8**.

Compound 40A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.62 - 0.81 (m, 1 H) 1.22 - 1.32 (m, 1 H) 1.35 - 1.59 (m, 2 H) 1.60 - 1.79 (m, 1 H) 1.79 - 2.10 (m, 1 H) 2.45 - 2.55 (m, 1 H) 2.52 - 2.66 (m, 1 H) 2.69 - 2.86 (m, 1 H) 3.92 (br t, *J*=12.9 Hz, 1 H) 4.29 (d, *J*=13.6 Hz, 1 H) 5.00 (br d, *J*=13.6 Hz, 1 H) 5.44 (br d, *J*=7.6 Hz, 1 H) 5.75 (s, 1 H) 6.97 (br d, *J*=7.9 Hz, 1 H) 7.11 - 7.22 (m, 2 H) 7.25 (t, *J*=7.1 Hz, 1 H) 7.34 (t, *J*=7.4 Hz, 1 H) 7.55 (d, *J*=7.9 Hz, 1 H) 7.59 - 7.69 (m, 1 H) 7.99 (d, *J*=7.6 Hz, 1 H) 8.34 (d, *J*=4.1 Hz, 1 H) 11.29 (br s, 1 H) LC/MS (method LC-C): R_t 2.54 min, MH⁺ 417

$[\alpha]_D^{20}$: -445.38° (c 0.119, DMF)

Chiral HPLC (method HPLC-B): R_t 4.30 min, chiral purity 100%.

Synthesis of Compound 40B:

- 5 (17**S*)-4-hydroxy-16-(pyridin-2-yl)-7,8,9,10,11,16-hexahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **40B**, 76 mg) was obtained using the procedure described for compound **8**.

Compound 40B:

- 10 ^1H NMR (500 MHz, DMSO- d_6) δ ppm 0.78 (br q, $J=12.6$ Hz, 1 H) 1.28 – 1.38 (m, 1 H) 1.40 - 1.56 (m, 2 H) 1.63 - 1.84 (m, 1 H) 1.94 - 2.10 (m, 1 H) 2.51 - 2.57 (m, 1 H) 2.64 (br d, $J=13.6$ Hz, 1 H) 2.83 (br t, $J = 11.7$ Hz, 1 H) 3.99 (br t, $J=12.9$ Hz, 1 H) 4.36 (d, $J=13.6$ Hz, 1 H) 5.08 (br d, $J=13.6$ Hz, 1 H) 5.52 (d, $J=7.6$ Hz, 1 H) 5.82 (s, 1 H) 7.05 (d, $J=7.6$ Hz, 1 H) 7.16 - 7.51 (m, 4 H) 7.52 - 7.76 (m, 2 H) 8.06 (d, $J=7.6$ Hz, 1 H) 8.41 (br d, $J=4.4$ Hz, 1 H) 11.31 (br s, 1 H)
- 15

LC/MS (method LC-C): R_t 2.54 min, MH^+ 417

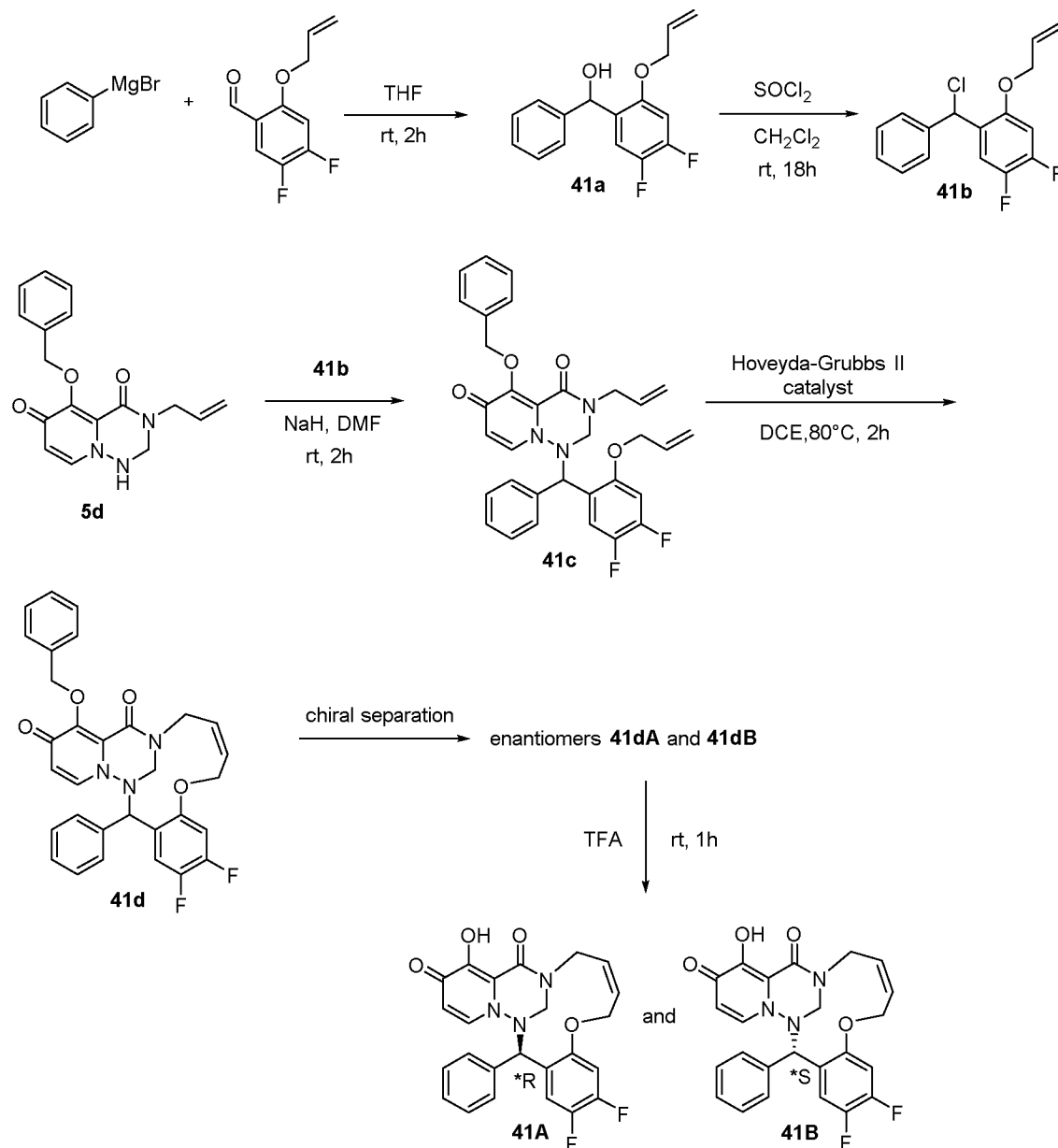
$[\alpha]_D^{20}$: +410.05° (c 0.189, DMF)

Chiral HPLC (method HPLC-B): R_t 4.97 min, chiral purity 100%.

20

Example 41: synthesis of (18**R,Z*)-2,3-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18_H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **41A**) and (18**S,Z*)-2,3-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18_H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

- 25 (compound **41B**)



Synthesis of intermediate **41a**:

At 0°C under N_2 , phenylmagnesium bromide [CAS 100-58-3] (13 mL, 13 mmol) was added dropwise to a solution of 2-(allyloxy)-4,5-difluorobenzaldehyde [CAS 1698016-61-3] (2.5 g, 13 mmol) in THF (20 mL). The mixture was stirred at rt for 2 h. The reaction was quenched at 0°C with a saturated aqueous solution of NH_4Cl and the aqueous phase was extracted with EtOAc. The organic layer was washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 μm , 80 g, heptane/EtOAc from 90/10 to 80/20). The pure fractions were collected and concentrated to dryness to give (2-(allyloxy)-4,5-difluorophenyl)(phenyl)methanol (intermediate **41a**, 3 g).

Synthesis of intermediate 41b:

1-(allyloxy)-2-(chloro(phenyl)methyl)-4,5-difluorobenzene (intermediate **41b**, 3.2 g) was obtained using the procedure described for intermediate **5a**.

5 Synthesis of intermediate 41c:

3-allyl-1-((2-(allyloxy)-4,5-difluorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **41c**, 1.5 g) was obtained using the procedure described for intermediate **5e**.

10 Synthesis of intermediate 41d:

(**Z*)-12-(benzyloxy)-2,3-difluoro-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **41d**, 340 mg) was obtained using the procedure described for intermediate **5f**.

15 The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OJ-H 5 µm 250 x 30 mm, Mobile phase: 65% CO₂, 35% MeOH) to give the first eluted enantiomer **41dA** (141 mg) and the second eluted enantiomer **41dB** (129 mg).

Synthesis of Compound 41A:

20 18**R,Z*)-2,3-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **41A**, 75 mg) was obtained using the procedure described for intermediate **5A**.

25 Compound 41A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.00 - 3.13 (m, 1 H) 4.20 - 4.35 (m, 2 H) 4.57 - 4.79 (m, 2 H) 5.03 (d, *J*=13.9 Hz, 1 H) 5.11 - 5.24 (m, 1 H) 5.42 (d, *J*=7.6 Hz, 1 H) 5.85 - 6.01 (m, 1 H) 6.01 - 6.17 (m, 1 H) 6.99 - 7.20 (m, 5 H) 7.26 (br d, *J*=7.6 Hz, 1 H) 7.35 - 7.45 (m, 1 H) 8.12 (br t, *J*=10.6 Hz, 1 H)

30 LC/MS (method LC-C): R_t 2.64 min, MH⁺ 452

[α]_D²⁰: +562.39° (c 0.234, DMF)

Chiral HPLC (method HPLC-A): R_t 4.37 min, chiral purity 100%.

Synthesis of Compound 41B:

35 18**S,Z*)-2,3-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **41B**, 66 mg) was obtained using the procedure described for intermediate **5A**.

Compound 41B:

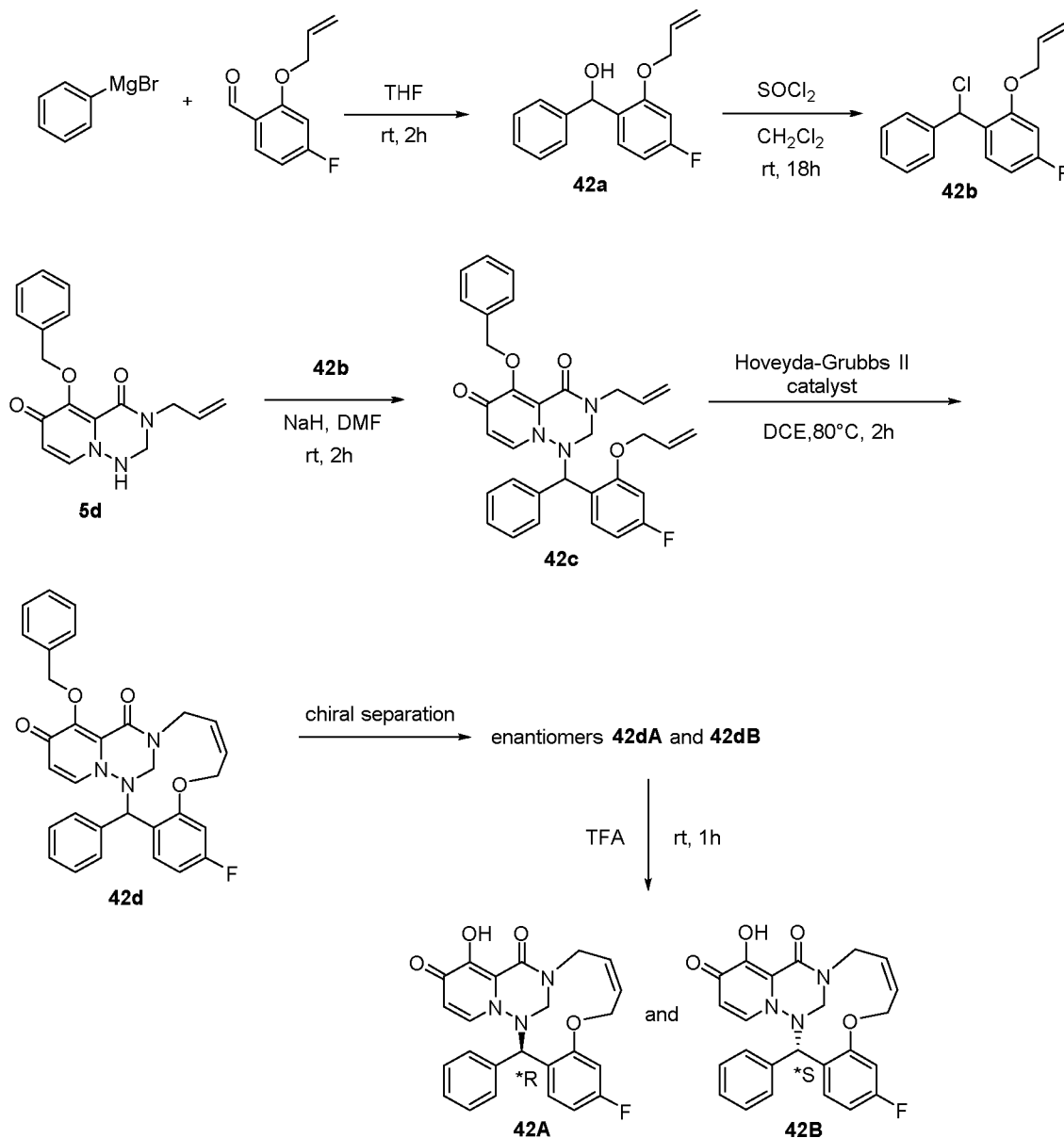
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.07 - 3.13 (m, 1 H) 4.10 - 4.43 (m, 2 H) 4.46 - 4.78 (m, 2 H) 5.03 (d, *J*=13.9 Hz, 1 H) 5.18 (br s, 1 H) 5.42 (d, *J*=7.57 Hz, 1 H) 5.79 - 6.22 (m, 2 H) 7.05 - 7.19 (m, 5 H) 7.26 (br d, *J*=7.3 Hz, 1 H) 7.40 (br dd, *J*=11.8, 7.4 Hz, 1 H) 8.12 (br t, *J*=10.6 Hz, 1 H)

LC/MS (method LC-C): *R*_t 2.64 min, MH⁺ 452

[α]_D²⁰: -660.41° (c 0.245, DMF)

Chiral HPLC (method HPLC-A): *R*_t 5.36 min, chiral purity 100%.

Example 42: synthesis of (18**R,Z*)-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **42A**) and (18**S,Z*)-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **42B**)



Synthesis of intermediate **42a**:

(2-(allyloxy)-4-fluorophenyl)(phenyl)methanol (intermediate **42a**, 2.4 g) was obtained using the procedure described for intermediate **41a** starting from 2-(allyloxy)-4-fluorobenzaldehyde [CAS 1207288-81-0] (11.655 mmol) and phenylmagnesiumbromide [CAS 100-58-3].

Synthesis of intermediate **42b**:

2-(allyloxy)-1-(chloro(phenyl)methyl)-4-fluorobenzene (intermediate **42b**, 2.6 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 42c:

3-allyl-1-((2-(allyloxy)-4-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **42c**, 2.05 g) was obtained using the procedure described for intermediate **5e**.

5

Synthesis of intermediate 42d:

(Z)-12-(benzyloxy)-3-fluoro-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **42d**, 330 mg) was obtained using the procedure described for intermediate **5f**.

10

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OJ-H 5 µm 250 x 30 mm, Mobile phase: 55% CO₂, 45% EtOH) to give the first eluted enantiomer (146 mg) and the second eluted enantiomer (128 mg). The two enantiomers were further purified by flash chromatography over silica gel (15-40 µm, 4 g, CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and concentrated to dryness to give enantiomer **42dA** (120 mg) and enantiomer **42dB** (90 mg).

15

Synthesis of Compound 42A:

(18*R,Z)-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **42A**, 62 mg) was obtained using the procedure described for compound **5A**.

20

Compound 42A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.19 (br dd, *J*=13.9, 8.5 Hz, 1 H) 4.23 (d, *J*=13.9 Hz, 1 H) 4.39 (br t, *J*=8.4 Hz, 1 H) 1 H) 4.69 - 4.83 (m, 2 H) 5.10 (d, *J*=13.9 Hz, 1 H) 5.27 (s, 1 H) 5.48 (d, *J*=7.9 Hz, 1 H) 5.98 (br s, 1 H) 6.08 - 6.22 (m, 1 H) 7.04 - 7.29 (m, 8 H) 8.14 (t, *J*=7.7 Hz, 1 H)

25

LC/MS (method LC-C): R_t 2.56 min, MH⁺ 434

[α]_D²⁰: +613.19° (c 0.235, DMF)

30

Chiral HPLC (method HPLC-B): R_t 4.88 min, chiral purity 100%.

Synthesis of Compound 42B:

(18*S,Z)-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **42B**, 52 mg) was obtained using the procedure described for compound **5A**.

35

Compound 42B:

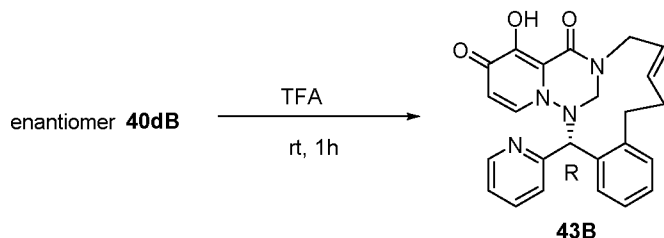
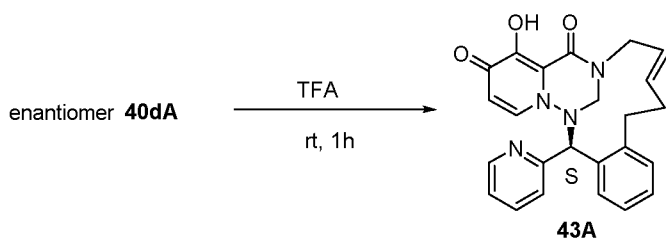
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.19 (br dd, *J*=13.7, 8.4 Hz, 1 H) 4.23 (d, *J*=13.9 Hz, 1 H) 4.39 (br t, *J*=8.4 Hz, 1 H) 4.71 - 4.82 (m, 2 H) 5.10 (d, *J*=13.9 Hz, 1 H) 5.27 (s, 1 H) 5.48 (d, *J*=7.9 Hz, 1 H) 5.98 (br s, 1 H) 6.08 - 6.20 (m, 1 H) 7.06 - 7.29 (m, 8 H) 8.14 (t, *J*=7.6 Hz, 1 H)

LC/MS (method LC-C): R_t 2.56 min, MH⁺ 434

[α]_D²⁰: -645.56° (c 0.248, DMF)

Chiral HPLC (method HPLC-B): R_t 6.18 min, chiral purity 100%.

- 10 **Example 43:** synthesis of (17*S,E*)-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **43A**) and (17*R,E*)-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **43B**)

**Synthesis of Compound 43A:**

(17*S,E*)-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **43A**, 150 mg) was obtained using the procedure described for compound **5A**.

Compound 43A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.89 - 2.11 (m, 1 H) 2.50 - 2.60 (m, 3 H) 3.05 - 3.14 (m, 1 H) 4.29 (br d, *J*=13.6 Hz, 1 H) 4.51 - 4.83 (m, 1 H) 5.13 (br d, *J*=13.6 Hz, 1 H) 5.29 - 5.59 (m, 3 H) 5.92 (dt, *J*=15.16, 7.6 Hz, 1 H) 7.03 - 7.25 (m, 3 H) 7.33 (br t, *J*=7.1 Hz, 1 H) 7.37 - 7.51 (m, 2 H) 7.52 - 7.80 (m, 1 H) 8.11 (br d, *J*=8.1 Hz, 1 H) 8.34 (br d, *J*=4.0 Hz, 1 H)

LC/MS (method LC-B): R_t 2.42 min, MH^+ 415

$[\alpha]_D^{20}$: -724.29° (c 0.140, DMF)

Chiral HPLC (method HPLC-A): R_t 4.67 min, chiral purity 100%.

5 **Synthesis of Compound 43B:**

(17*R,E*)-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **43B**, 147 mg) was obtained using the procedure described for compound **5A**.

10 **Compound 43B:**

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.92 - 2.16 (m, 1 H) 2.53 - 2.74 (m, 3 H) 2.97 - 3.16 (m, 1 H) 4.29 (br d, $J=13.6$ Hz, 1 H) 4.71 (br dd, $J=13.6, 4.6$ Hz, 1 H) 5.13 (br d, $J=13.6$ Hz, 1 H) 5.32 - 5.60 (m, 3 H) 5.92 (dt, $J=15.28, 7.8$ Hz, 1 H) 7.07 - 7.27 (m, 3 H) 7.33 (br t, $J=7.1$ Hz, 1 H) 7.37 - 7.50 (m, 2 H) 7.64 (br t, $J=7.3$ Hz, 1 H) 8.11 (br d, $J=7.6$ Hz, 1 H) 8.34 (br d, $J=4.0$ Hz, 1 H)

LC/MS (method LC-B): R_t 2.42 min, MH^+ 415

$[\alpha]_D^{20}$: +685.48° (c 0.124, DMF)

Chiral HPLC (method HPLC-A): R_t 5.40 min, chiral purity 100%.

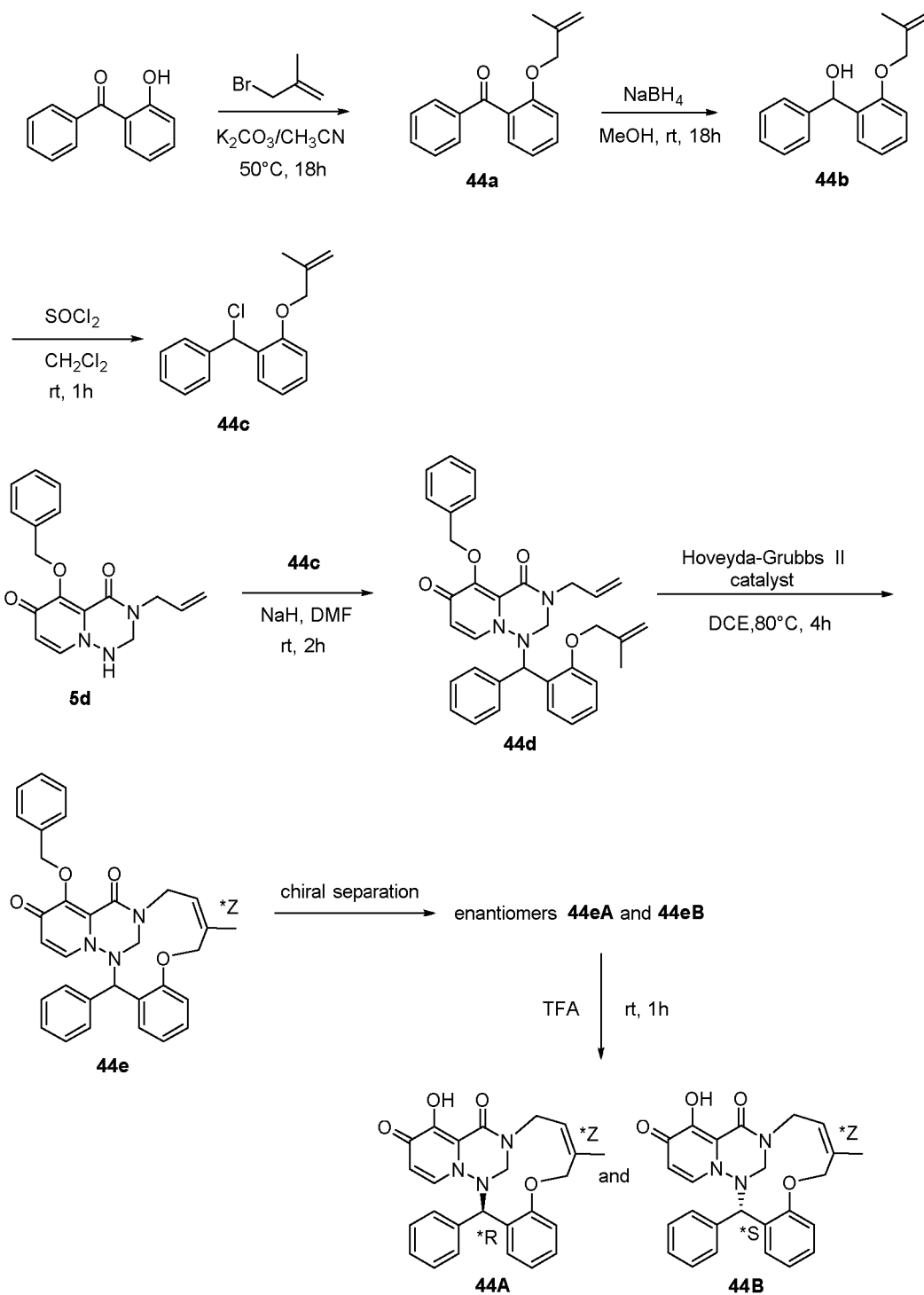
20

Example 44: synthesis of (18**R*,**Z*)-12-hydroxy-7-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **44A**) and (18**S*,**Z*)-12-hydroxy-7-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

25

(Compound **44B**)

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Synthesis of intermediate **44a**:

(2-((2-methylallyl)oxy)phenyl)(phenyl)methanone (intermediate **44a**, 5.1 g) was obtained using the procedure described for intermediate **20a** starting from (2-hydroxyphenyl)(phenyl)methanone [CAS 117-99-7] (20.179 mmol) and 3-bromo-2-methylprop-1-ene [CAS 1458-98-6] (22.197 mmol).

Synthesis of intermediate 44b:

(2-((2-methylallyl)oxy)phenyl)(phenyl)methanol (intermediate 44b, 5.2 g) was obtained using the procedure described for intermediate 11b.

5 Synthesis of intermediate 44c:

1-(chloro(phenyl)methyl)-2-((2-methylallyl)oxy)benzene (intermediate 44c, 1.3 g) was obtained using the procedure described for intermediate 5a.

Synthesis of intermediate 44d:

- 10 3-allyl-5-(benzyloxy)-1-((2-((2-methylallyl)oxy)phenyl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate 44d, 1.7 g) was obtained using the procedure described for intermediate 5e.

Synthesis of intermediate 44e:

- 15 (*Z)-12-(benzyloxy)-7-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate 44e, 500 mg) was obtained using the procedure described for intermediate 5f.

- 20 The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 30 mm, Mobile phase: 55% CO₂, 45% EtOH) to give the first eluted enantiomer 44eA (194 mg) and the second eluted enantiomer 44eB (202 mg).

Synthesis of Compound 44A:

- 25 (18*R,*Z)-12-hydroxy-7-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound 44A, 115 mg) was obtained using the procedure described for intermediate 5A.

Compound 44A:

- 30 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.97 (s, 3 H) 3.28 (br dd, *J*=13.9, 7.6 Hz, 1 H) 4.17 - 4.23 (m, 2 H) 4.72 (d, *J*=11.0 Hz, 1 H) 4.95 (br dd, *J*=14.0, 7.4 Hz, 1 H) 5.07 (d, *J*=13.6 Hz, 1 H) 5.14 (s, 1 H) 5.42 (br t, 7.3 Hz, 1H) 5.47 (d, *J*=7.6 Hz, 1 H) 7.02 - 7.26 (m, 7 H) 7.29 - 7.40 (m, 1 H) 7.38 - 7.51 (m, 1 H) 8.13 (dd, *J*=7.6, 1.26 Hz, 1 H)
LC/MS (method LC-C): R_t 2.63 min, MH⁺ 430
35 [α]_D²⁰: -784.62° (c 0.117, DMF)
Chiral HPLC (method HPLC-B): R_t 6.56 min, chiral purity 100%.

Synthesis of Compound 44B:

(18^{*}*S*, ^{*}*Z*)-12-hydroxy-7-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **44B**, 109 mg) was obtained using the procedure described for intermediate **5A**.

Compound 44B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.97 (s, 3 H) 3.24 - 3.32 (m, 1 H) 4.13 - 4.36 (m, 2 H) 4.72 (d, *J*=11.0 Hz, 1 H) 4.95 (dd, *J*=14.0, 7.4 Hz, 1 H) 5.00 - 5.17 (m, 2 H) 5.42 (br t, *J*=7.3 Hz, 1 H) 5.46 - 5.52 (m, 1 H) 6.80 - 7.28 (m, 7 H) 7.32 - 7.39 (m, 1 H) 7.38 - 7.78 (m, 1 H) 8.13 (dd, *J*=7.57, 1.26 Hz, 1 H)

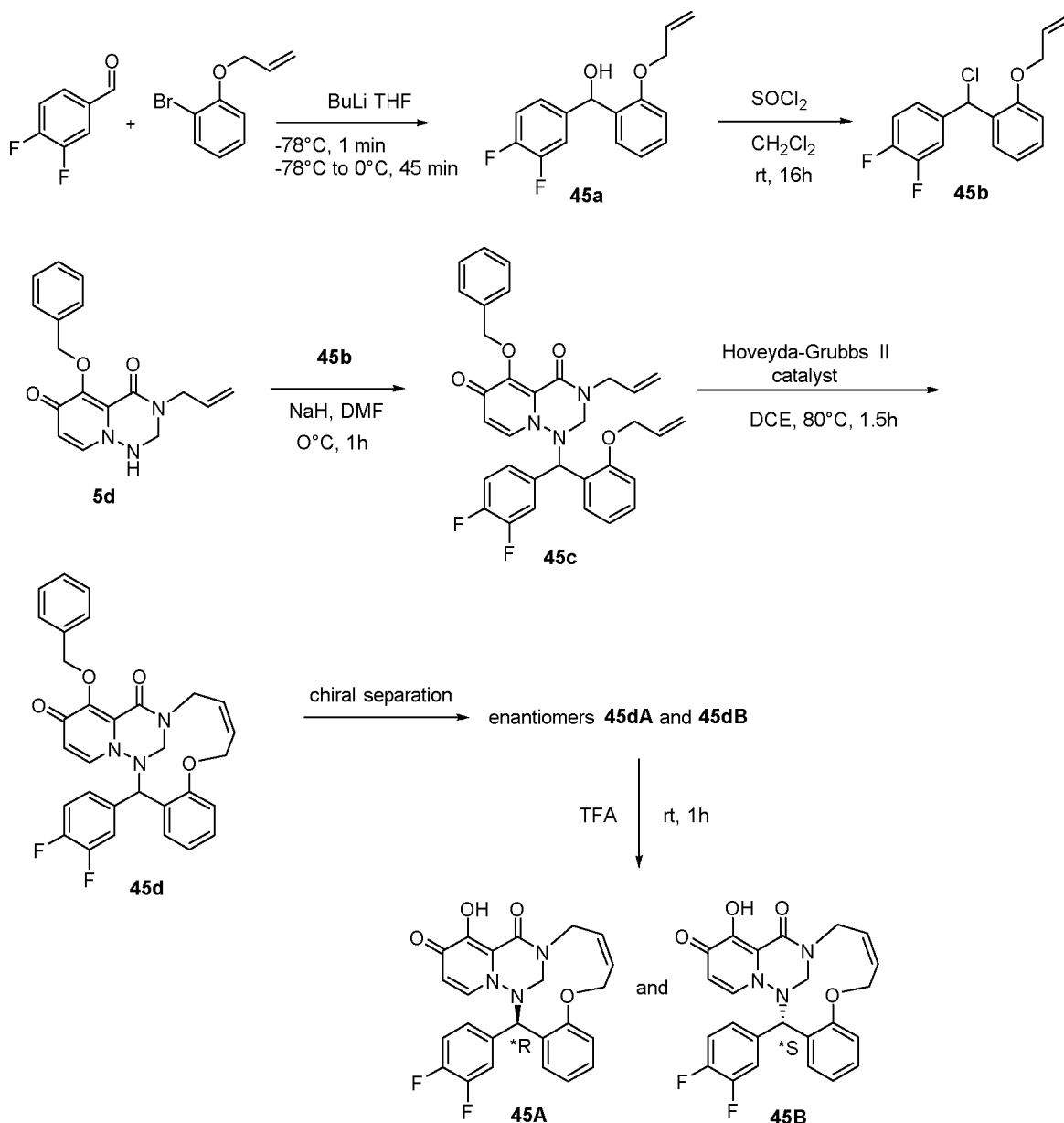
LC/MS (method LC-C): R_t 2.63 min, MH⁺ 430

[α]_D²⁰: +687.07° (c 0.147, DMF)

Chiral HPLC (method HPLC-B): R_t 5.00 min, chiral purity 100%.

Example 45: synthesis of (18^{*}*R*,*Z*)-18-(3,4-difluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **45A**) and (18^{*}*S*,*Z*)-18-(3,4-difluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **45B**)

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**Synthesis of intermediate 45d:**

(Z)-12-(benzyloxy)-18-(3,4-difluorophenyl)-6,9-dihydro-18H-10,17-

5 methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(intermediate 45d, 130 mg) was obtained using the procedures described in example 5.

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel[®] OD-H 5 μm 250 x 20 mm, Mobile phase: 85% CO₂, 15% MeOH) to give the first eluted enantiomer 45dA (49 mg) and the second eluted enantiomer 45dB (47 mg).

10

Synthesis of Compound 45A:

(18*R,Z)-18-(3,4-difluorophenyl)-12-hydroxy-6,9-dihydro-18H-10,17-

methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **45A**, 26 mg) was obtained using the procedure described for compounds **5A**.

Compound 45A:

- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.11 (br dd, *J*=13.7, 8.4 Hz, 1 H) 4.13 (d, *J*=13.6 Hz, 1 H) 4.18 - 4.39 (m, 1 H) 4.63 - 4.76 (m, 2 H) 5.04 (d, *J*=13.9 Hz, 1 H) 5.25 (s, 1 H) 5.56 (d, *J*=7.6 Hz, 1 H) 5.59 - 5.93 (m, 1 H) 5.93 - 6.20 (m, 1 H) 6.94 (br s, 1 H) 7.15 - 7.24 (m, 2 H) 7.25 - 7.40 (m, 4 H) 8.01 (br d, *J*=7.6 Hz, 1 H)
LC/MS (method LC-C): R_t 2.60 min, MH⁺ 452
10 [α]_D²⁰: +609.39° (c 0.181, DMF)
Chiral HPLC (method HPLC-B): R_t 4.55 min, chiral purity 100%.

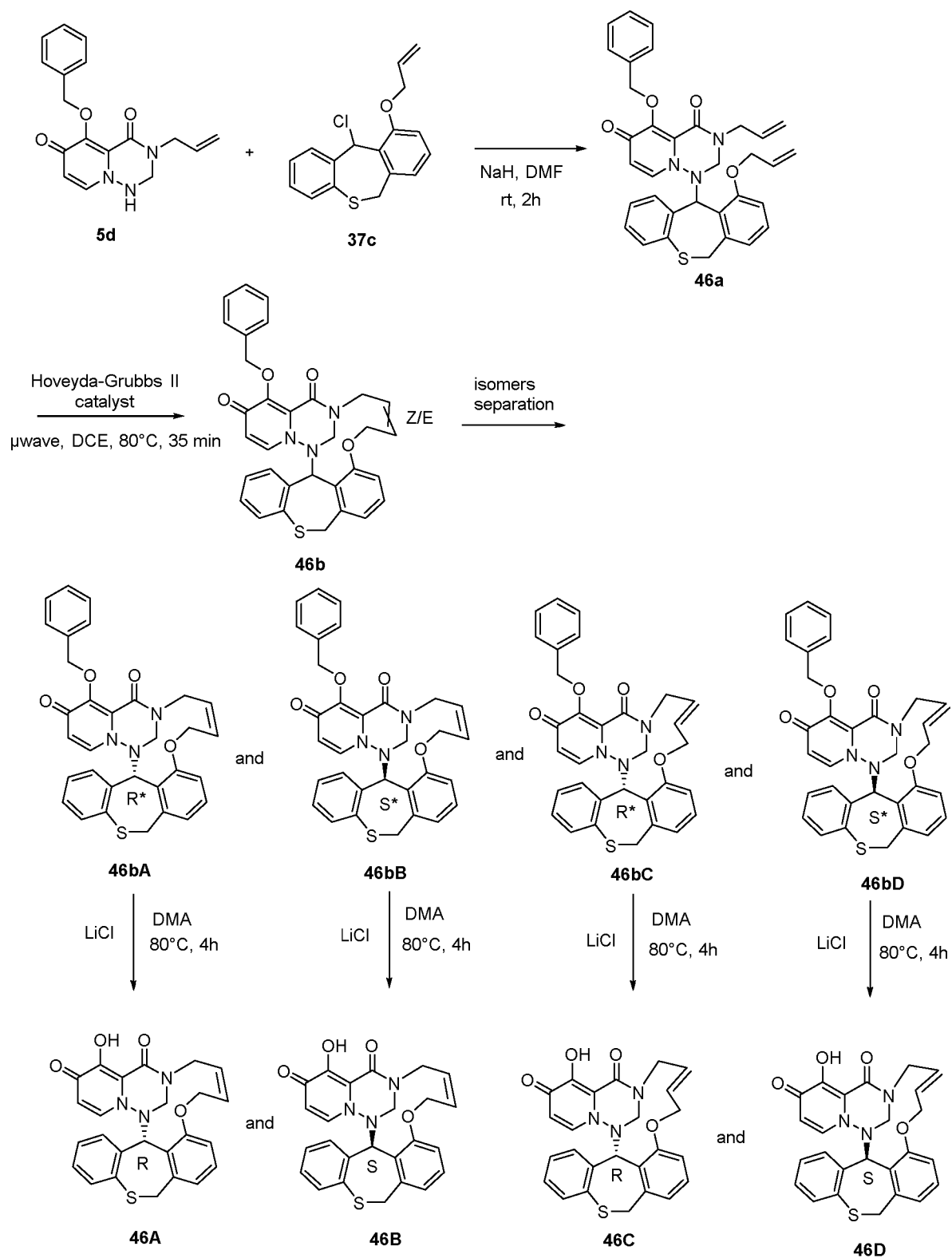
Synthesis of Compound 45B:

- (18^{*}*S,Z*)-18-(3,4-difluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-
15 methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **45B**, 25 mg) was obtained using the procedure described for compounds **5A**.

Compound 45B:

- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.11 (br dd, *J*=13.9, 8.2 Hz, 1 H) 4.13 (d, *J*=13.6 Hz, 1 H) 4.18 - 4.29 (m, 1 H) 4.64 - 4.76 (m, 2 H) 5.04 (d, *J*=13.6 Hz, 1 H) 5.25 (s, 1 H) 5.56 (d, *J*=7.6 Hz, 1 H) 5.72-5.85 (m, 1 H) 6.03 - 6.14 (m, 1 H) 6.94 (br s, 1 H) 7.15 - 7.23 (m, 2 H) 7.25 - 7.40 (m, 4 H) 8.02 (br d, *J*=7.9 Hz, 1 H)
LC/MS (method LC-C): R_t 2.60 min, MH⁺ 452
25 [α]_D²⁰: -634.06° (c 0.138, DMF)
Chiral HPLC (method HPLC-B): R_t 6.17 min, chiral purity 100%.

- Example 46: synthesis of (21*R,Z*)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-
(epirop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-
30 *f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **46A**), (21*S,Z*)-16-hydroxy-
6,10,13,21a-tetrahydro-7,8-(epirop[1]en[1]yl[3]ylidene)-14,21-
methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-
dione (compound **46B**), (17*R,E*)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-
(epirop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-
35 *f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **46C**) and (17*S,E*)-12-
hydroxy-2,6,9,17a-tetrahydro-3,4-(epirop[1]en[1]yl[3]ylidene)-10,17-
methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-
dione (Compound **46D**)



Synthesis of intermediate 46a:

- Under N₂, at 0°C, NaH (60% dispersion in mineral oil) (2.11 g, 52.74 mmol) was added to a solution of 3-allyl-5-(benzyloxy)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-

dione (intermediate **5d**, 10.95 g, 35.16 mmol) in DMF (250 mL). The mixture was stirred for 30 min at 0°C. 10-(allyloxy)-11-chloro-6,11-dihydrodibenzo[*b,e*]thiepine (intermediate **37c**, 11.18 g, 36.92 mmol) in DMF (50 mL) was added and the mixture was stirred at rt for 2 h. The reaction was quenched by the addition of ice and water. The mixture was extracted with EtOAc and the combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated to dryness. The residue was taken up with a minimum amount of EtOAc. The precipitate was filtered off and dried to give a first batch of 3-allyl-1-(10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **46a**, 12.5 g). The filtrate was concentrated under reduced pressure. Purification of the residue was carried out by flash chromatography over silica gel (30 µm, 220 g, CH₂Cl₂/CH₃OH from 99/1 to 96/4). The fractions containing the expected compound were collected and concentrated to dryness. This fraction was taken up with EtOAc and the precipitate was filtered off to give a second batch of intermediate **46a** (2.65 g).

Synthesis of intermediate **46b**:

The reaction was performed in an Anton-Paar microwave oven in 4 batches of 3.47 g of intermediate **46a**.

A degassed solution of 3-allyl-1-(10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **46a**, 13.9 g, 24.06 mmol) and Hoveyda-Grubbs catalyst 2nd generation [CAS 301224-40-8] (3.0 g, 4.81 mmol) in dry DCE (1.5 L) was stirred at 80°C for 35 min. SiliaMetS[®] DMT (31.5 g, 19.25 mmol) was added and the mixture was stirred at rt for 18 h. The reaction mixture was filtered through celite[®]. The celite[®] was washed with CH₂Cl₂ and the filtrate was concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (30 µm, 330 g, CH₂Cl₂/CH₃OH from 99.5/0.5 to 97/3). A second purification was carried out by flash chromatography over silica gel (15 µm, 120 g, Toluene/*i*PrOH 93/7). The pure fractions were collected and concentrated under reduced pressure to afford 16-(benzyloxy)-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepin[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (mixture of *Z* and *E* isomers, intermediate **46b**, 1.98 g).

The isomers were separated via chiral SFC (Stationary phase: Chiralcel[®] OJ-H 5 µm 250 x 30 mm, Mobile phase: 65% CO₂, 35% MeOH) to give the first eluted isomer **46bA** (460 mg), a mixture of **46bB** and **46bC** (790 mg) and finally the last eluted isomer **46bB** (340 mg). The isomers **46bB** (382 mg) and **46bC** (306 mg) were separated via chiral SFC (Stationary phase: Chiralpak[®] AS-H 5 µm 250 x 20 mm, Mobile phase: 40% CO₂, 60% MeOH).

Synthesis of compound 46A:

(21*R,Z*)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epiprop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **46A**, 258 mg) was obtained using the procedure described for Compound **37A**.

Compound 46A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.75 - 3.86 (m, 2 H) 4.15 - 4.26 (m, 1 H) 4.32 (d, *J*=13.2 Hz, 1 H) 4.51 - 4.58 (m, 1 H) 4.85 (dd, *J*=10.6, 6.8 Hz, 1 H) 5.02 (d, *J*=13.2 Hz, 1 H) 5.61 (d, *J*=7.9 Hz, 1 H) 5.72 (d, *J*=13.9 Hz, 1 H) 6.08 (s, 1 H) 6.29 (dt, *J*=10.5, 7.2 Hz, 1 H) 6.37 - 6.43 (m, 1 H) 6.57 (d, *J*=6.9 Hz, 1 H) 6.81 (t, *J*=7.4 Hz, 1 H) 7.01 - 7.14 (m, 3 H) 7.20 (d, *J*=8.1 Hz, 1 H) 7.26 (d, *J*=7.7 Hz, 1 H) 7.40 (t, *J*=7.9 Hz, 1 H)
LC/MS (method LC-C): R_t 2.66 min, MH⁺ 460
[α]_D²⁰: +252.22° (c 0.293, DMF)

Synthesis of compound 46B:

(21*S,Z*)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epiprop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **46B**, 235 mg) was obtained using the procedure described for Compound **37A**.

Compound 46B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.75 - 3.86 (m, 2 H) 4.18 (dd, *J*=13.6, 7.6 Hz, 1 H) 4.32 (d, *J*=13.2 Hz, 1 H) 4.55 (dd, *J*=10.7, 7.9 Hz, 1 H) 4.85 (dd, *J*=10.4, 6.9 Hz, 1 H) 5.02 (d, *J*=13.2 Hz, 1 H) 5.61 (d, *J*=7.6 Hz, 1 H) 5.72 (d, *J*=13.9 Hz, 1 H) 6.08 (s, 1 H) 6.29 (dt, *J*=10.6, 7.3 Hz, 1 H) 6.37 - 6.43 (m, 1 H) 6.57 (d, *J*=6.9 Hz, 1 H) 6.81 (t, *J*=7.5 Hz, 1 H) 7.06 - 7.14 (m, 3 H) 7.20 (d, *J*=8.1 Hz, 1 H) 7.26 (d, *J*=7.7 Hz, 1 H) 7.40 (t, *J*=7.9 Hz, 1 H)
LC/MS (method LC-C): R_t 2.66 min, MH⁺ 460
[α]_D²⁰: -271.76° (c 0.262, DMF)

Synthesis of compound 46C:

(17*R,E*)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **46C**, 155 mg) was obtained using the procedure described for Compound **37A**.

Compound 46C:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.17 (dd, *J*=14.0, 8.4 Hz, 1 H) 3.87 (d, *J*=13.6 Hz, 1 H) 4.25 (d, *J*=13.9 Hz, 1 H) 4.41 - 4.51 (m, 1 H) 4.70 - 4.83 (m, 2 H) 5.15 (d, *J*=13.6 Hz, 1 H) 5.41 (s, 1 H) 5.61 (d, *J*=7.9 Hz, 1 H) 5.82 (d, *J*=13.2 Hz, 1 H) 5.90 - 6.01 (m, 1 H) 6.17 - 6.27 (m, 1 H) 6.77 - 6.82 (m, 1 H) 6.82 - 6.88 (m, 1 H) 7.00 - 7.06 (m, 1 H) 7.07 - 7.13 (m, 1 H) 7.19 (d, *J*=7.6 Hz, 1 H) 7.23 (d, *J*=8.2 Hz, 1 H) 7.34 (d, *J*=7.9 Hz, 1 H) 7.37 - 7.44 (m, 1 H) 11.26 (br s, 1 H)

LC/MS (method LC-C): R_t 2.56 min, MH⁺ 460

[α]_D²⁰: +513.07° (c 0.306, DMF)

Chiral HPLC (method HPLC-B): R_t 7.30 min, chiral purity 100%

Synthesis of compound 46D:

(17*S,E*)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **46D**, 160 mg) was obtained using the procedure described for compound **37A**.

Compound 46D:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.17 (dd, *J*=14.0, 8.4 Hz, 1 H) 3.87 (d, *J*=13.6 Hz, 1 H) 4.25 (d, *J*=13.9 Hz, 1 H) 4.43 - 4.50 (m, 1 H) 4.73 - 4.81 (m, 2 H) 5.15 (d, *J*=13.9 Hz, 1 H) 5.41 (s, 1 H) 5.61 (d, *J*=7.6 Hz, 1 H) 5.82 (d, *J*=13.6 Hz, 1 H) 5.91 - 6.00 (m, 1 H) 6.22 (dt, *J*=15.5, 7.7 Hz, 1 H) 6.79 - 6.88 (m, 2 H) 7.04 (d, *J*=7.8 Hz, 1 H) 7.10 (t, *J*=7.5 Hz, 1 H) 7.19 (d, *J*=7.4 Hz, 1 H) 7.23 (d, *J*=8.1 Hz, 1 H) 7.34 (d, *J*=7.6 Hz, 1 H) 7.40 (t, *J*=7.9 Hz, 1 H) 11.23 (br s, 1 H)

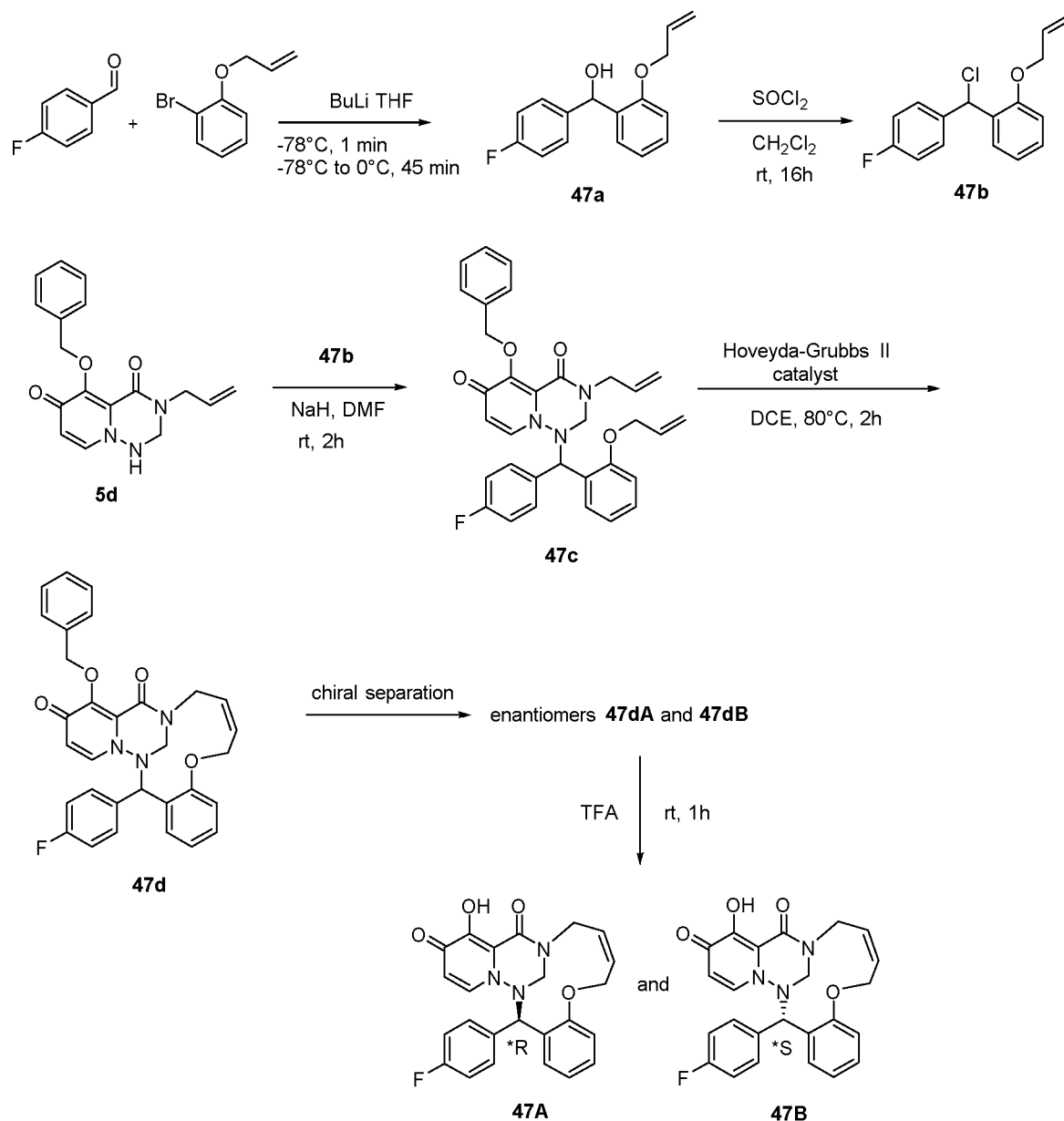
LC/MS (method LC-C): R_t 2.56 min, MH⁺ 460

[α]_D²⁰: -512.94° (c 0.255, DMF)

Chiral HPLC (method HPLC-B): R_t 8.94 min, chiral purity 100%

Example 47: synthesis of (18**R,Z*)-18-(4-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **47A**) and (18**S,Z*)-18-(4-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **47B**)

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**Synthesis of intermediate 47d:**

(Z)-12-(benzyloxy)-18-(4-fluorophenyl)-6,9-dihydro-18*H*-10,17-

5 methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(intermediate 47d, 130 mg) was obtained using the procedures described in example 5.

The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OJ-H 5 μm 250 x 30 mm, Mobile phase: 75% CO₂, 25% MeOH) to give the first eluted enantiomer 47dA (242 mg) and the second eluted enantiomer 47dB (243 mg).

10

Synthesis of Compound 47A:

(18**R*,*Z*)-18-(4-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-

methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **47A**, 100 mg) was obtained using the procedure described for Compound **5A**.

Compound 47A:

- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.19 (dd, *J*=13.9, 8.5 Hz, 1 H) 4.20 - 4.32 (m, 2 H) 4.72 - 4.81 (m, 2 H) 5.11 (d, *J*=13.6 Hz, 1 H) 5.32 (s, 1 H) 5.56 (d, *J*=7.6 Hz, 1 H) 5.82-5.94 (m, 1 H) 6.09 - 6.19 (m, 1 H) 7.02 (br t, *J*=8.7 Hz, 2 H) 7.20 - 7.33 (m, 4 H) 7.30 - 7.37 (m, 1 H) 7.42 (t, *J*=7.7 Hz, 1 H) 8.08 (br d, *J*=7.6 Hz, 1 H) 10.94 (br s, 1 H)
LC/MS (method LC-C): R_t 2.52 min, MH⁺ 434
10 [α]_D²⁰: +685.14° (c 0.148, DMF)
Chiral HPLC (method HPLC-B): R_t 4.89 min, chiral purity 100%.

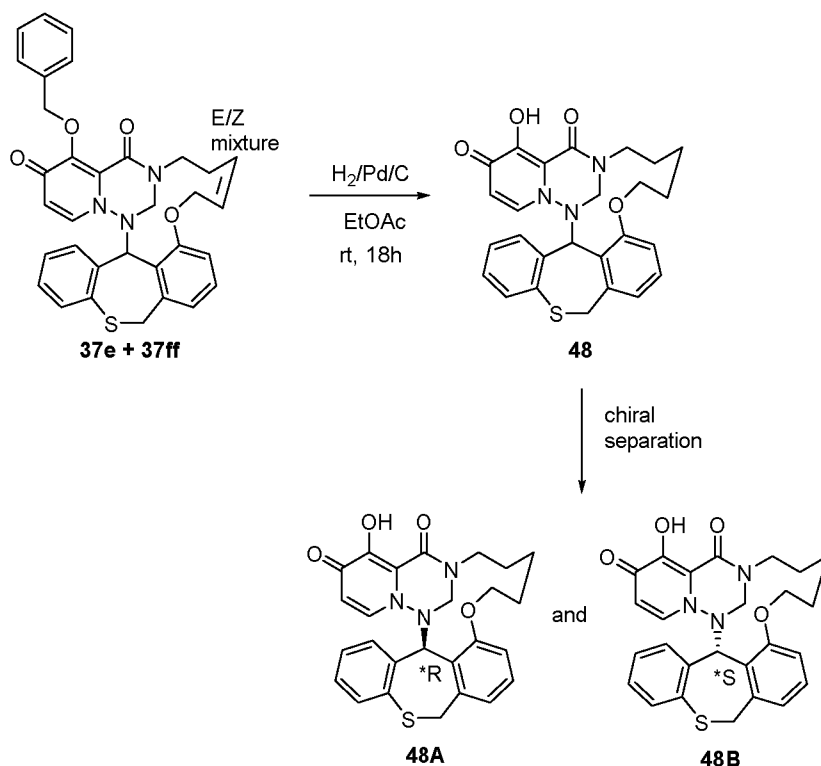
Synthesis of Compound 47B:

- (18^{*}*S,Z*)-18-(4-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-
15 methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **47B**, 113 mg) was obtained using the procedure described for Compound **5A**.

Compound 47B:

- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.19 (br dd, *J*=13.9, 8.5 Hz, 1 H) 4.22 (d, *J*=13.6 Hz, 1 H) 4.25 - 4.37 (m, 1 H) 4.70 - 4.82 (m, 2 H) 5.11 (d, *J*=13.9 Hz, 1 H) 5.32 (s, 1 H) 5.56 (d, *J*=7.6 Hz, 1 H) 5.85 - 5.95 (m, 1 H) 6.09 - 6.19 (m, 1 H) 7.02 (br t, *J*=8.5 Hz, 2 H) 7.12 - 7.27 (m, 4 H) 7.30 - 7.37 (m, 1 H) 7.38 - 7.47 (m, 1 H) 8.08 (br d, *J*=7.3 Hz, 1 H) 10.90 (br s, 1 H)
25 LC/MS (method LC-C): R_t 2.52 min, MH⁺ 434
[α]_D²⁰: -706.56° (c 0.122, DMF)
Chiral HPLC (method HPLC-B): R_t 5.85 min, chiral purity 100%.

Example 48: synthesis of Compounds **48**, **48A** and **48B**



Synthesis of Compound 48:

Under an atmospheric pressure of H_2 , a mixture of intermediates **37e** + **37f** (undefined Z/E mixture, 222 mg, 0.39 mmol) and Pd/C (10%) (210 mg, 0.197 mmol) in EtOAc (12 mL) was stirred at rt for 18 h. The catalyst was removed by filtration through celite[®]. The celite[®] was washed with EtOAc and then with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography over silica gel (15 μm , 12 g, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ from 99/1 to 93/7) to give, after freeze-drying in $\text{CH}_3\text{CN}/\text{water}$, Compound **48** (112 mg).

The two enantiomers were separated via chiral HPLC (Stationary phase: Chiralpak[®] IG, 20 μm , 250 g, Mobile phase: EtOH + 0.1% TFA) to give, after freeze-drying in water/ CH_3CN (2/8), the first eluted enantiomer **48A** (33 mg) and the second eluted enantiomer **48B** (34 mg).

Compound 48A:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 1.16 - 1.30 (m, 1 H) 1.36 - 1.44 (m, 1 H) 1.55 - 1.70 (m, 2 H) 1.82 - 1.93 (m, 1 H) 2.04 - 2.16 (m, 1 H) 2.82 (br d, $J=13.6$ Hz, 1 H) 3.82 - 3.91 (m, 2 H) 4.13 (br t, $J=12.6$ Hz, 1 H) 4.29 (d, $J=13.2$ Hz, 1 H) 4.33 - 4.40 (m, 1 H) 5.01 (d, $J=13.2$ Hz, 1 H) 5.65 (d, $J=7.9$ Hz, 1 H) 5.87 (d, $J=13.6$ Hz, 1 H) 6.05 (s, 1 H) 6.73 (d, $J=7.6$ Hz, 1 H) 6.84 (t, $J=7.3$ Hz, 1 H) 6.99 - 7.08 (m, 3 H) 7.08 - 7.15 (m, 1 H) 7.36 (t, $J=7.9$ Hz, 1 H) 7.46 (d, $J=7.6$ Hz, 1 H) 11.82 (br s, 1 H)

LC/MS (method LC-C): R_t 2.85 min, MH^+ 476

$[\alpha]_D^{20}$: +174.8° (c 0.127, DMF)

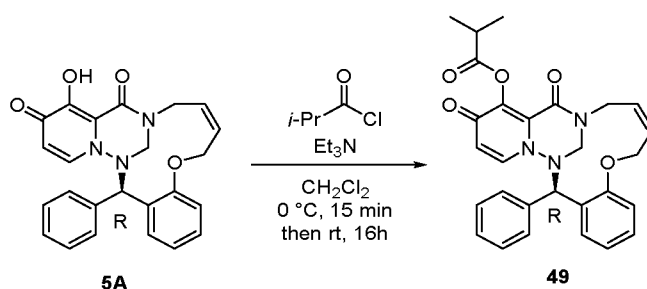
Compound 48B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.20 - 1.29 (m, 1 H) 1.36 - 1.44 (m, 1 H) 1.55 - 1.71 (m, 2 H) 1.82 - 1.93 (m, 1 H) 2.05 - 2.16 (m, 1 H) 2.82 (br d, *J*=13.9 Hz, 1 H) 3.81 - 3.90 (m, 2 H) 4.13 (br t, *J*=12.5 Hz, 1 H) 4.29 (d, *J*=13.6 Hz, 1 H) 4.33 - 4.40 (m, 1 H) 5.01 (d, *J*=13.6 Hz, 1 H) 5.64 (d, *J*=7.6 Hz, 1 H) 5.87 (d, *J*=13.6 Hz, 1 H) 6.05 (s, 1 H) 6.73 (d, *J*=7.3 Hz, 1 H) 6.84 (t, *J*=7.4 Hz, 1 H) 7.00 - 7.07 (m, 3 H) 7.08 - 7.13 (m, 1 H) 7.36 (t, *J*=7.9 Hz, 1 H) 7.46 (d, *J*=7.6 Hz, 1 H) 11.81 (br s, 1 H)

LC/MS (method LC-C): *R*_t 2.84 min, MH⁺ 476

[α]_D²⁰: -184° (c 0.125, DMF)

Example 49: synthesis of (18*R,Z*)-11,13-dioxo-18-phenyl-6,9,11,13-tetrahydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecin-12-yl isobutyrate (Compound 49)

**Synthesis of Compound 49:**

Et₃N (45.2 μL, 325 μmol) was added to a solution of compound **5A** (90.0 mg, 217 μmol) in CH₂Cl₂ (9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and isobutyryl chloride [CAS 79-30-1] (27.2 μL, 0.26 mmol) was added dropwise. The reaction mixture was stirred at rt overnight. The mixture was evaporated under vacuum. Purification was carried out by flash chromatography over silica gel (30 μm, 12 g, CH₂Cl₂/MeOH 99/1). The residue was taken up in CH₃CN/MeOH. The solid was filtered off and dried under vacuum at 65 °C overnight to give (18*R,Z*)-11,13-dioxo-18-phenyl-6,9,11,13-tetrahydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecin-12-yl isobutyrate (compound **49**, 71 mg).

Compound 49:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.10 (br d, *J*=7.6 Hz, 1H), 7.41 - 7.46 (m, 1H), 7.35 (t, *J*=7.3 Hz, 1H), 7.28 - 7.38 (m, 1H), 7.24 (d, *J*=7.9 Hz, 1H), 7.16 - 7.22 (m, 3H), 7.10 (br s, 2H), 6.02 - 6.15 (m, 1H), 5.92 (br s, 1H), 5.76 (s, 1H), 5.68 (br d, *J*=7.3 Hz, 1H), 5.31 (s, 1H), 5.14 (d, *J*=13.9 Hz, 1H), 4.70 - 4.75 (m, 1H), 4.68 (br dd, *J*=13.9, 4.7

Hz, 1H), 4.26 - 4.35 (m, 1H), 4.22 (d, $J=13.9$ Hz, 1H), 3.16 (dd, $J=13.6, 8.5$ Hz, 1H), 2.77 (spt, $J=7.0$ Hz, 1H), 1.24 (br d, $J=6.9$ Hz, 6H).

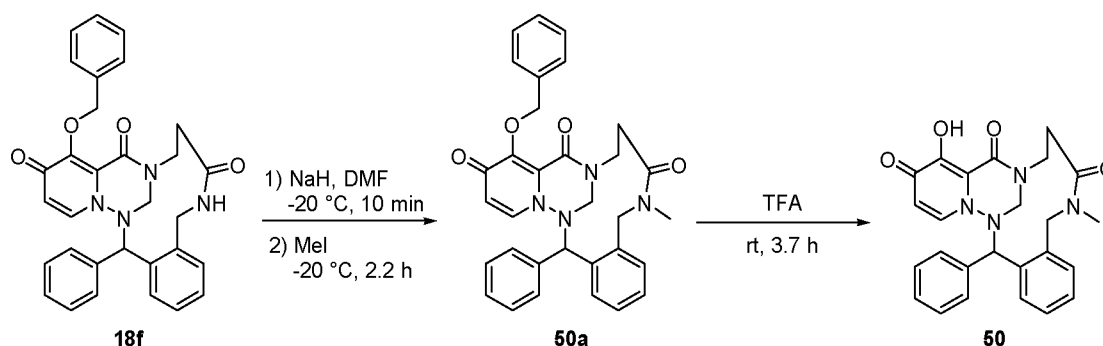
LC/MS (method LC-A): Rt 2.71 min, MH^+ 486

$[\alpha]_D^{20}$: -628.76° (c 0.153, DMF)

5 Chiral SFC (method SFC-A): Rt 1.62 min, chiral purity 100%.

Example 50: synthesis of 12-hydroxy-6-methyl-18-phenyl-5,8,9,18-tetrahydro-10,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5,9]tetraazacyclotridecine-7,11,13(6*H*)-trione (Compound **50**)

10



100/0 to 0/100). The residue was lyophilized (dioxane/H₂O) and purified a last time by flash chromatography on silica-C18 (H₂O/MeOH from 100/0 to 0/100) to give 12-hydroxy-6-methyl-18-phenyl-5,8,9,18-tetrahydro-10,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5,9]tetraazacyclotridecine-7,11,13(6*H*)-trione (compound **50**, 74 mg).

5

Compound 50:

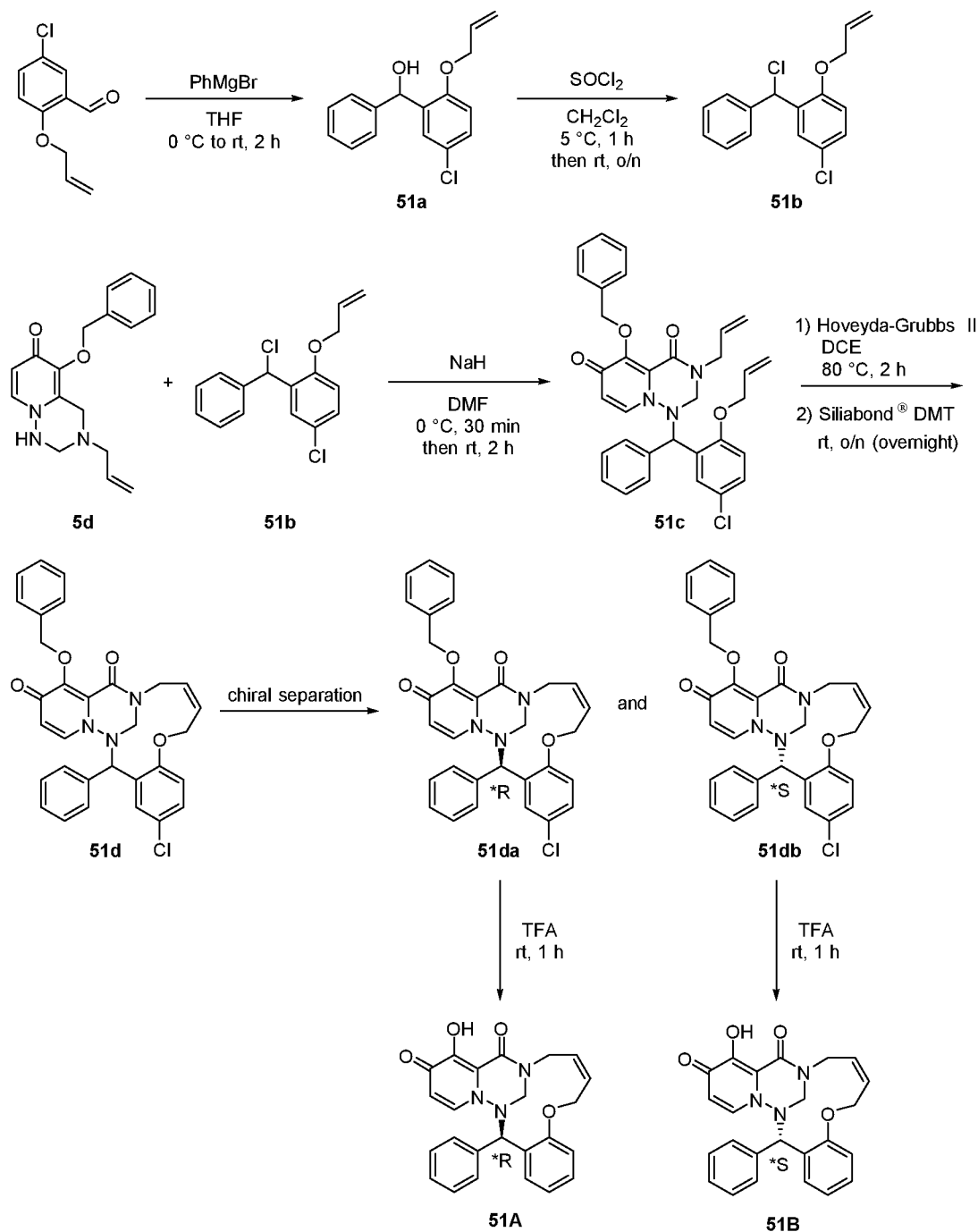
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.65 (m, 1H), 8.36 (d, *J*=7.8 Hz, 1H), 7.50 - 7.64 (m, 1H), 7.43 (d, *J*=7.6 Hz, 1H), 7.29 - 7.41 (m, 4H), 7.14 - 7.23 (m, 3H), 5.82 (s, 1H), 5.56 (d, *J*=13.7 Hz, 1H), 5.43 (d, *J*=7.6 Hz, 1H), 5.09 (d, *J*=13.1 Hz, 1H), 3.99 (d, *J*=13.1 Hz, 1H), 3.74 - 3.86 (m, 1H), 3.41 (br d, *J*=13.7 Hz, 1H), 3.08 - 3.21 (m, 3H), 2.86 (s, 3H)

10

Example 51: synthesis of (18**R,Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **51A**) and (18**S,Z*)-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **51B**)

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Synthesis of intermediate 51a:

(2-(allyloxy)-5-chlorophenyl)(phenyl)methanol (intermediate **51a**, 2.63 g) was obtained using the procedure described for intermediate **21a**. The desired intermediate **51a** was purified by flash chromatography over silica gel (20-45 μm , 120 g, heptane/EtOAc 90/10).

Synthesis of intermediate 51b:

1-(allyloxy)-4-chloro-2-(chloro(phenyl)methyl)benzene (intermediate **51b**, 2.2 g) was obtained using the procedure described for intermediate **5a**.

5 Synthesis of intermediate 51c:

3-allyl-1-((2-(allyloxy)-5-chlorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **51c**, 1.74 g) was obtained using the procedure described for intermediate **5e**.

10 Synthesis of intermediates 51d, 51da and 51db:

(Z)-12-(benzyloxy)-2-chloro-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **51d**, 374 mg) was obtained using the procedure described for intermediate **5f**. A second purification was performed by preparative LC (Stationary phase: irregular bare silica 40 g, Mobile phase: heptane/MeOH/EtOAc 60/5/35).

The enantiomers (330 mg) were separated via chiral SFC (Stationary phase: Chiracel OJ-H 5 μ m 250*30mm, Mobile phase: 75% CO₂, 25% MeOH) to afford the first eluted enantiomer **51da** (113 mg) and the second eluted enantiomer **51db** (115 mg).

20 Synthesis of compound 51A:

(18*R,Z)-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **51A**, 60 mg) was obtained using the procedure described for compound **5A**.

25 Compound 51A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.16 (d, *J*=1.9 Hz, 1H), 7.46 (dd, *J*=8.8, 2.5 Hz, 1H), 7.37 (br d, *J*=7.6 Hz, 1H), 7.28 (d, *J*=8.8 Hz, 1H), 7.20 (br d, *J*=2.2 Hz, 3H), 7.09 - 7.22 (m, 2H), 6.08 - 6.19 (m, 1H), 5.97 (br s, 1H), 5.47 (d, *J*=7.6 Hz, 1H), 5.29 (s, 1H), 5.13 (d, *J*=13.9 Hz, 1H), 4.71 - 4.81 (m, 2H), 4.31 - 4.37 (m, 1H), 4.29 (d, *J*=13.6 Hz, 1H), 3.20 (br dd, *J*=13.7, 8.4 Hz, 1H).

LC/MS (method LC-C): Rt 2.70 min, MH⁺ 450

$[\alpha]_D^{20}$: +809.44 ° (c 0.119, DMF)

Chiral HPLC (method HPLC-B): Rt 5.28 min, chiral purity 100%

35 Synthesis of compound 51B:

(18*S,Z)-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **51B**, 52 mg) was obtained using the procedure described for compound **5A**.

Compound 51B:

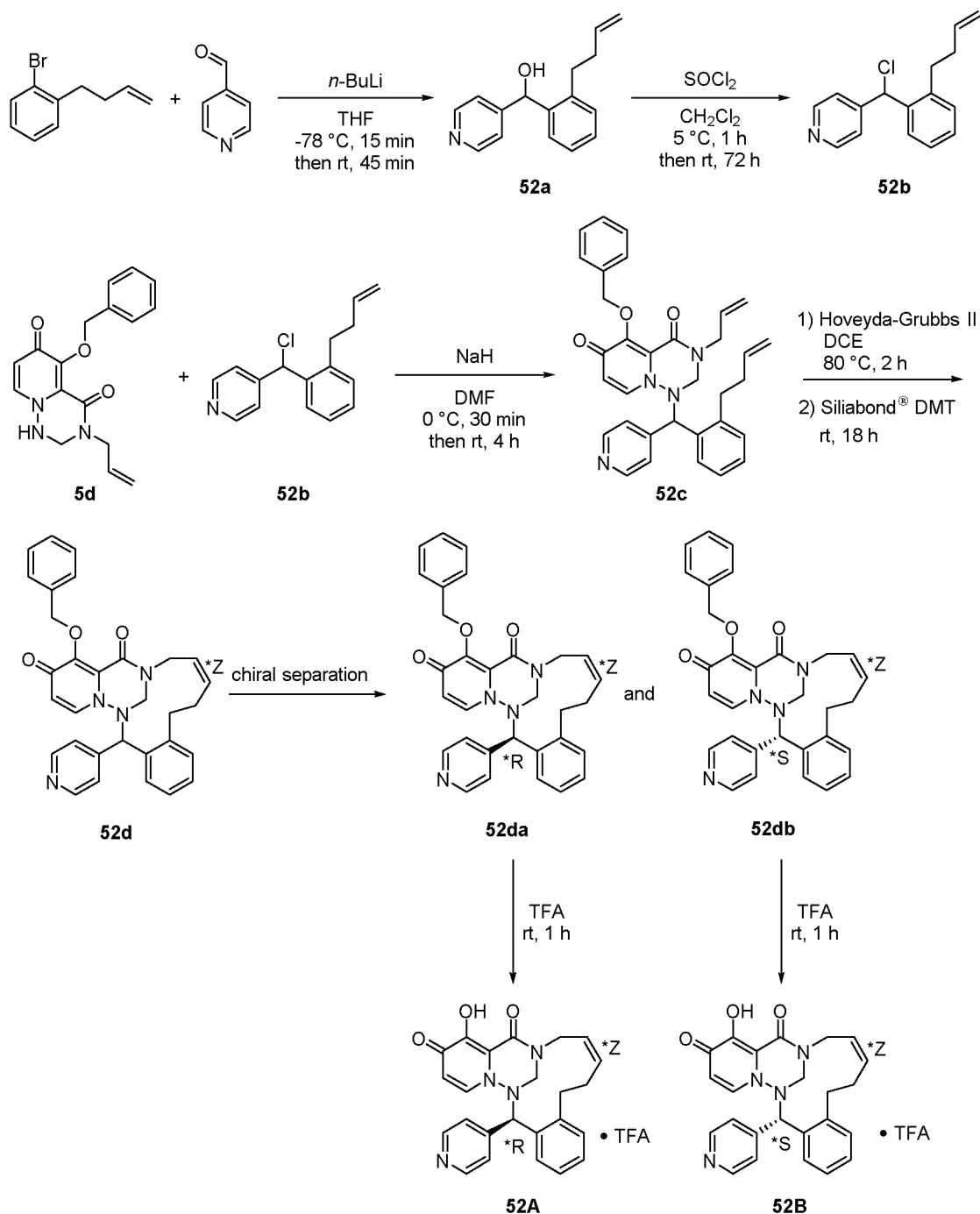
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.16 (d, *J*=2.0 Hz, 1H), 7.46 (dd, *J*=8.8, 2.8 Hz, 1H), 7.38 (br d, *J*=7.6 Hz, 1H), 7.28 (d, *J*=8.6 Hz, 1H), 7.10 - 7.24 (m, 5H), 6.08 - 6.20 (m, 1H), 5.98 (br s, 1H), 5.47 (d, *J*=7.6 Hz, 1H), 5.29 (s, 1H), 5.13 (d, *J*=14.1 Hz, 1H), 4.70 - 4.82 (m, 2H), 4.24 - 4.37 (m, 1H), 4.29 (d, *J*=13.6 Hz, 1H), 3.17 - 3.25 (m, 1H).

LC/MS (method LC-C): Rt 2.70 min, MH⁺ 450

[α]_D²⁰: -785.86 ° (c 0.151, DMF)

Chiral HPLC (method HPLC-B): Rt 6.42 min, chiral purity 100%

Example 52: synthesis of (16^{*R},^{*Z})-4-hydroxy-16-(pyridin-4-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **52A**) and (16^{*S},^{*Z})-4-hydroxy-16-(pyridin-4-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **52B**)



Synthesis of intermediate 52a:

(2-(but-3-en-1-yl)phenyl)(pyridin-4-yl)methanol (intermediate **52a**, 1.4 g) was obtained using the procedure described for intermediate **23a**. Crude intermediate **52a** was purified by preparative LC (Stationary phase: regular SiOH 30 μm 40 g, Mobile phase: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ from 100/0 to 98/2).

Synthesis of intermediate 52b:

4-((2-(but-3-en-1-yl)phenyl)chloromethyl)pyridine (intermediate **52b**, 1.4 g) was obtained using the procedure described for intermediate **5a**. Following the co-evaporation with toluene, the residue was suspended in EtOAc and the organic phase was washed with a 10% aqueous solution of K₂CO₃, dried over MgSO₄, filtered and concentrated to afford intermediate **52b**.

Synthesis of intermediate 52c:

3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)phenyl)(pyridin-4-yl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **52c**, 0.26 g) was obtained using the procedure described for intermediate **5e**.

Synthesis of intermediate 52d:

(*Z)-4-(benzyloxy)-16-(pyridin-4-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **52d**, 97 mg) was obtained using the procedure described for intermediate **5f**.

The enantiomers were separated via chiral SFC (Stationary phase: Whelk-O1 (*S,S*) 5 μ m 250*21.2 mm, Mobile phase: 40% CO₂, 60% EtOH) to afford the first eluted enantiomer **52da** (37 mg) and the second eluted enantiomer **52db** (37 mg).

Synthesis of compound 52A:

(16**R*,**Z*)-4-hydroxy-16-(pyridin-4-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[k]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione, trifluoroacetic acid (compound **52A**, 23 mg) was obtained using the procedure described for compound **5A**.

Compound 52A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.39 (d, *J*=5.1 Hz, 2H), 8.09 (d, *J*=7.6 Hz, 1H), 7.45 (t, *J*=7.3 Hz, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.26 - 7.33 (m, 3H), 7.22 (d, *J*=7.6 Hz, 1H), 5.94 - 6.06 (m, 1H), 5.51 (d, *J*=7.6 Hz, 1H), 5.41 - 5.49 (m, 1H), 5.23 (s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.71 (br dd, *J*=14.1, 5.1 Hz, 1H), 4.28 (d, *J*=13.6 Hz, 1H), 3.08 (br dd, *J*=13.9, 7.8 Hz, 1H), 2.58 - 2.66 (m, 1H), 2.53 - 2.57 (m, 2H), 1.93 - 2.05 (m, 1H).

LC/MS (method LC-C): Rt 2.29 min, MH⁺ 415

[α]_D²⁰: +546.88 ° (c 0.083, DMF)

Chiral HPLC (method HPLC-B): Rt 4.99 min, chiral purity 100%

Synthesis of compound 52B:

(16*S,*Z)-4-hydroxy-16-(pyridin-4-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione, trifluoroacetic acid (compound **52B**, 23 mg) was obtained using the procedure described for compound **5A**.

5

Compound 52B:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.39 (d, *J*=5.1 Hz, 2H), 8.09 (d, *J*=7.6 Hz, 1H), 7.45 (t, *J*=7.3 Hz, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.31 (br d, *J*=7.6 Hz, 3H), 7.22 (d, *J*=7.6 Hz, 1H), 5.93 - 6.06 (m, 1H), 5.51 (d, *J*=7.6 Hz, 1H), 5.41 - 5.49 (m, 1H), 5.23 (s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.71 (br dd, *J*=14.1, 5.1 Hz, 1H), 4.28 (d, *J*=13.6 Hz, 1H), 3.08 (br dd, *J*=13.9, 7.8 Hz, 1H), 2.52 - 2.65 (m, 3H), 1.94 - 2.05 (m, 1H).

10

LC/MS (method LC-C): Rt 2.29 min, MH⁺ 415

[α]_D²⁰: -547.15 ° (c0.118, DMF)

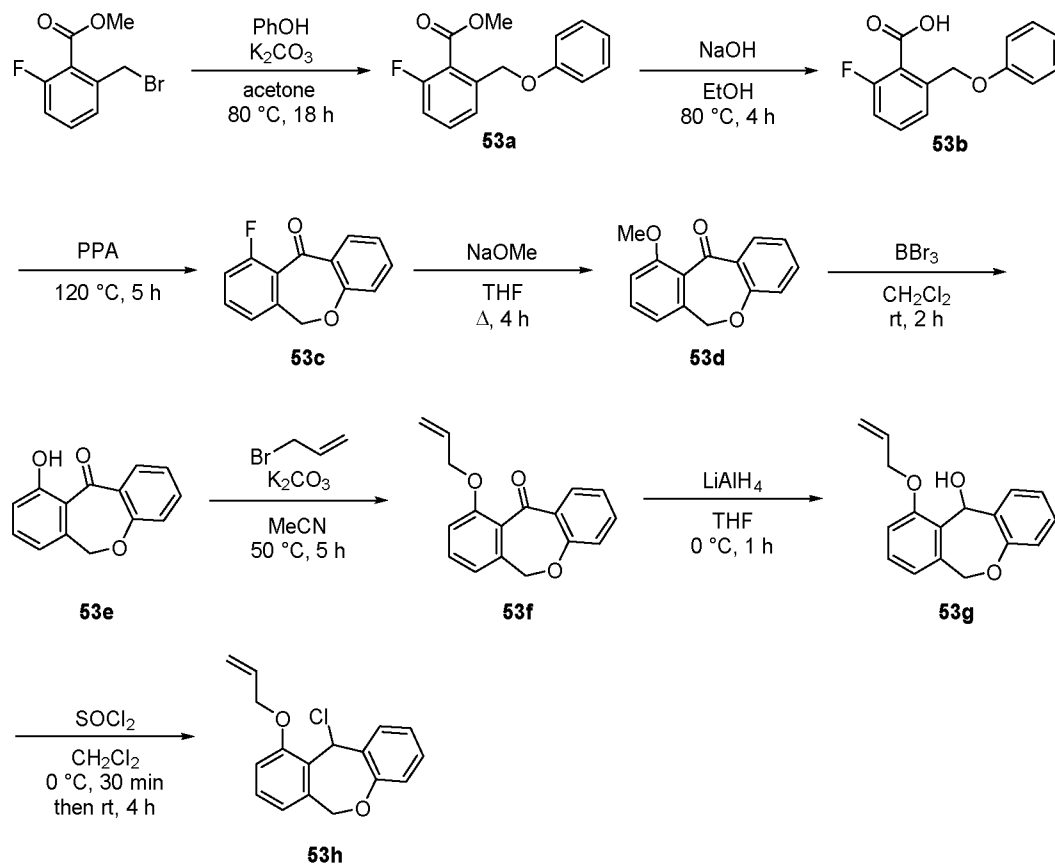
Chiral HPLC (method HPLC-B): Rt 5.92 min, chiral purity 100%

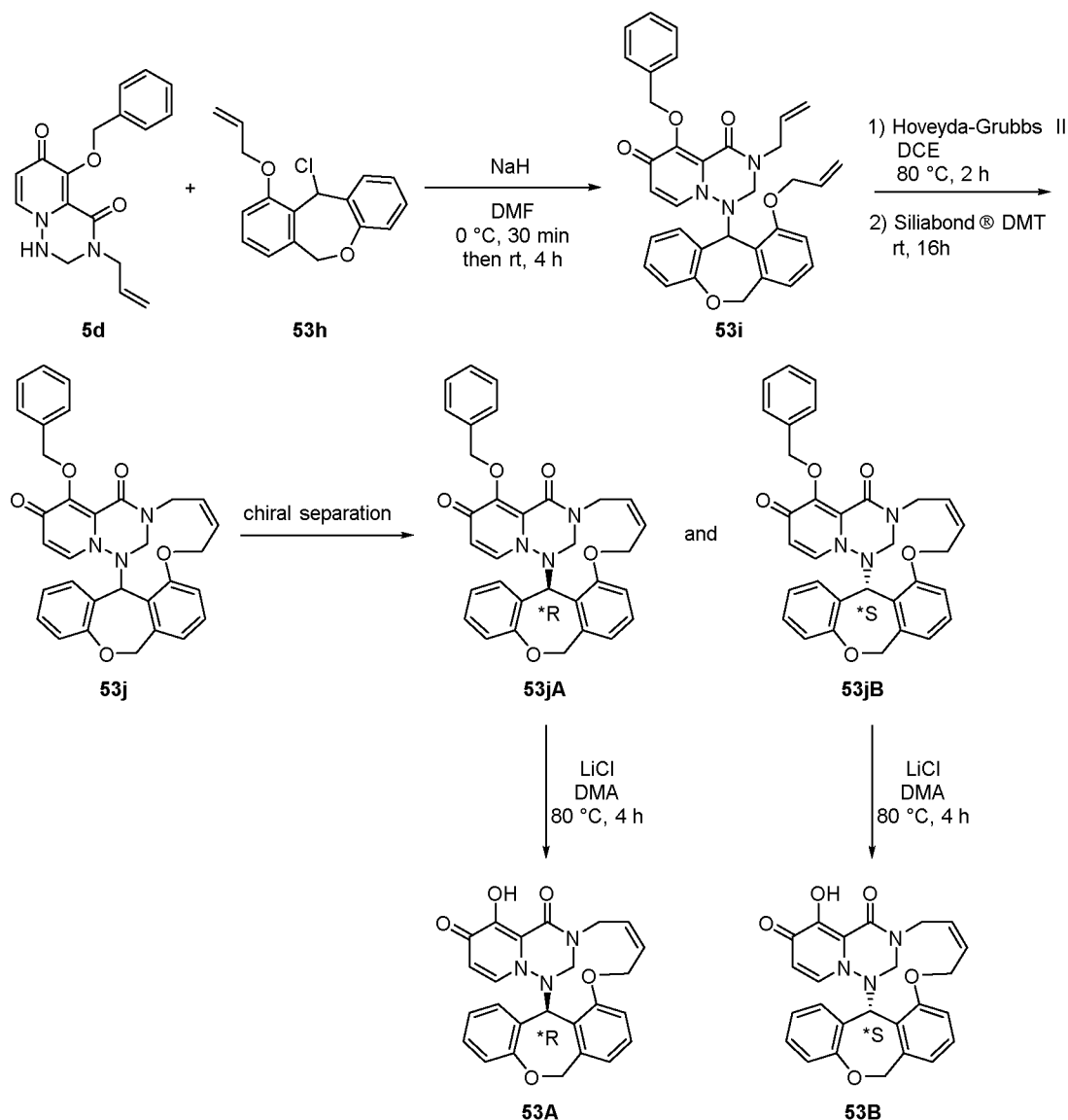
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Example 53: synthesis of (21a*R,*Z*)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epirop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]oxepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **53A**) and (21a*S,*Z*)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epirop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]oxepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **53B**)

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Synthesis of intermediate 53a:

Methyl 2-(bromomethyl)-6-fluorobenzoate [CAS 197516-58-8] (15.0 g, 60.7 mmol) was dissolved in acetone (230 mL). Phenol (5.71 g, 60.7 mmol) and K_2CO_3 (12.6 g, 91.1 mmol) were added and the reaction mixture was stirred at 80 °C for 18 h. The mixture was filtered and the solvent was evaporated under vacuum. Purification was carried out by flash chromatography over silica gel (20–45 μ m, 220 g, liquid injection (CH_2Cl_2 /heptane), heptane/EtOAc 90/10.). The pure fractions were collected and evaporated to dryness to afford methyl 2-fluoro-6-(phoxymethyl)benzoate (intermediate 53a, 5.55 g).

Synthesis of intermediate 53b:

A mixture of intermediate 53a (5.50 g, 21.1 mmol) and sodium hydroxide (2N in H_2O , 52.8 mL, 106 mmol) in EtOH (98.7 mL) was stirred at 80 °C for 4 h. The mixture was

diluted with water and acidified until pH 2 with HCl. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over MgSO₄, filtered and concentrated under vacuum to afford 2-fluoro-6-(phenoxymethyl)benzoic acid (intermediate **53b**, 5.24 g).

5

Synthesis of intermediate 53c:

Intermediate **53b** (5.24 g, 21.3 mmol) was added to polyphosphoric acid (8.30 g). The reaction mixture was stirred at 120 °C for 5 h. Iced water was added and the aqueous phase was extracted with EtOAc. The organic phase was dried over MgSO₄, filtered and
10 evaporated under vacuum. Purification was carried out by flash chromatography over silica gel (20-45 µm, 80 g, CH₂Cl₂ 100%). The pure fractions were collected and evaporated to dryness to afford 10-fluorodibenzo[*b,e*]oxepin-11(6*H*)-one (intermediate **53c**, 3.2 g).

15 **Synthesis of intermediate 53d:**

Intermediate **53c** (2.70 g, 11.8 mmol) was dissolved in THF (5.7 mL) and a solution of sodium methoxide (5.4 M, 13.8 mL, 74.5 mmol) was added. The reaction mixture was stirred under reflux for 4 h. An aqueous solution of HCl was added and the mixture was extracted with EtOAc. The organic phase was washed with water and brine, dried over
20 MgSO₄, filtered and the solvent was evaporated under vacuum. The residue was diluted with CH₂Cl₂ and few drops of heptane were added. The precipitated was filtered off and dried under vacuum to afford 10-methoxydibenzo[*b,e*]oxepin-11(6*H*)-one (intermediate **53d**, 1 g).

25 **Synthesis of intermediate 53e:**

To a solution of intermediate **53d** (1.00 g, 4.16 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added boron tribromide (8.32 mL, 8.32 mmol) dropwise. The reaction mixture was stirred at rt for 2 h. A saturated aqueous solution of sodium bicarbonate was added while the temperature of the mixture was maintained at 0 °C. The mixture was warmed up to
30 rt. Brine was added and the mixture was extracted with CH₂Cl₂. The organic phase was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated under vacuum. The residue was taken up in Et₂O. The solid was filtered off and dried under vacuum to afford 10-hydroxydibenzo[*b,e*]oxepin-11(6*H*)-one (intermediate **53e**, 220 mg).

35

Synthesis of intermediate 53f:

10-(allyloxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (intermediate **53f**, 1.05 g) was obtained using the procedure described for intermediate **37a**.

Synthesis of intermediate 53g:

10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]oxepin-11-ol (intermediate **53g**, 1.0 g) was obtained using the procedure described for intermediate **28b**.

5

Synthesis of intermediate 53h:

10-(allyloxy)-11-chloro-6,11-dihydrodibenzo[*b,e*]oxepine (intermediate **53h**, 1.0 g) was obtained using the procedure described for **5a**.

10 **Synthesis of intermediate 53i:**

3-allyl-1-(10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]oxepin-11-yl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **53i**, 1.21 g) was obtained using the procedure described for intermediate **5e**.

15 **Synthesis of intermediate 53j:**

(*Z*)-16-(benzyloxy)-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]oxepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (intermediate **53j**, 141 mg) was obtained using the procedure described for intermediate **5f**.

20 The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 μ m 250*30mm, Mobile phase: 50% CO₂, 50% EtOH) to give the first eluted enantiomer **53jA** (38 mg) and the second eluted enantiomer **53jB** (52 mg).

Synthesis of compound 53A:

25 LiCl (15.1 mg, 0.36 mmol) was added to a solution of intermediate **53jA** (38.0 mg, 71.2 μ mol) in DMA (0.4 mL) and the mixture was stirred at 80 °C for 4 h. The mixture was cooled to rt and evaporated in vacuo. Purification was carried out by flash chromatography over silica gel (15-40 μ m, 4 g, CH₂Cl₂/MeOH from 99/1 to 97.5/2.5). The pure fractions were collected and evaporated to dryness. The residue was freeze-dried (H₂O/CH₃CN 4/1) to afford (21a**R,Z*)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]oxepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (compound **53A**, 24 mg).

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Compound 53A:

35 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.66 (br s, 1H), 7.46 (t, *J*=7.8 Hz, 1H), 7.30 (d, *J*=7.6 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 1H), 7.19 (t, *J*=7.8 Hz, 1H), 7.13 (d, *J*=7.1 Hz, 1H), 6.83 (d, *J*=8.1 Hz, 1H), 6.62 (t, *J*=7.3 Hz, 1H), 6.33 - 6.46 (m, 3H), 6.29 (d, *J*=12.6 Hz, 1H), 5.76 (s, 1H), 5.55 (d, *J*=7.6 Hz, 1H), 4.97 (d, *J*=12.6 Hz, 1H), 4.96 (d, *J*=13.6 Hz,

1H), 4.75 - 4.83 (m, 1H), 4.66 (dd, $J=10.6, 6.1$ Hz, 1H), 4.25 (d, $J=13.1$ Hz, 1H), 4.11 (dd, $J=13.1, 7.6$ Hz, 1H), 3.80 (br dd, $J=13.1, 7.6$ Hz, 1H).

LC/MS (method LC-C): Rt 2.55 min, MH^+ 444

$[\alpha]_D^{20}$: -66.67° (c 0.108, DMF)

5 Chiral HPLC (method HPLC-B): Rt 6.89 min, chiral purity 100%

Synthesis of compound 53B:

(21a $^*S,Z$)-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epiprop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]oxepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (compound **53B**, 53 mg) was obtained using the procedure described for compound **53A**.

Compound 53B:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.46 (t, $J=7.7$ Hz, 1H), 7.31 (br d, $J=7.6$ Hz, 1H), 7.26 (d, $J=8.5$ Hz, 1H), 7.19 (br t, $J=7.6$ Hz, 1H), 7.14 (d, $J=7.3$ Hz, 1H), 6.83 (d, $J=8.2$ Hz, 1H), 6.57 - 6.66 (m, 1H), 6.25 - 6.47 (m, 4H), 5.76 (s, 1H), 5.56 (br d, $J=7.3$ Hz, 1H), 4.97 (br d, $J=12.6$ Hz, 2H), 4.79 (br dd, $J=10.6, 6.5$ Hz, 1H), 4.66 (br dd, $J=10.4, 6.6$ Hz, 1H), 4.26 (br d, $J=13.2$ Hz, 1H), 4.11 (br dd, $J=13.4, 7.4$ Hz, 1H), 3.80 (br dd, $J=12.8, 8.0$ Hz, 1H).

20 LC/MS (method LC-C): Rt 2.55 min, MH^+ 444

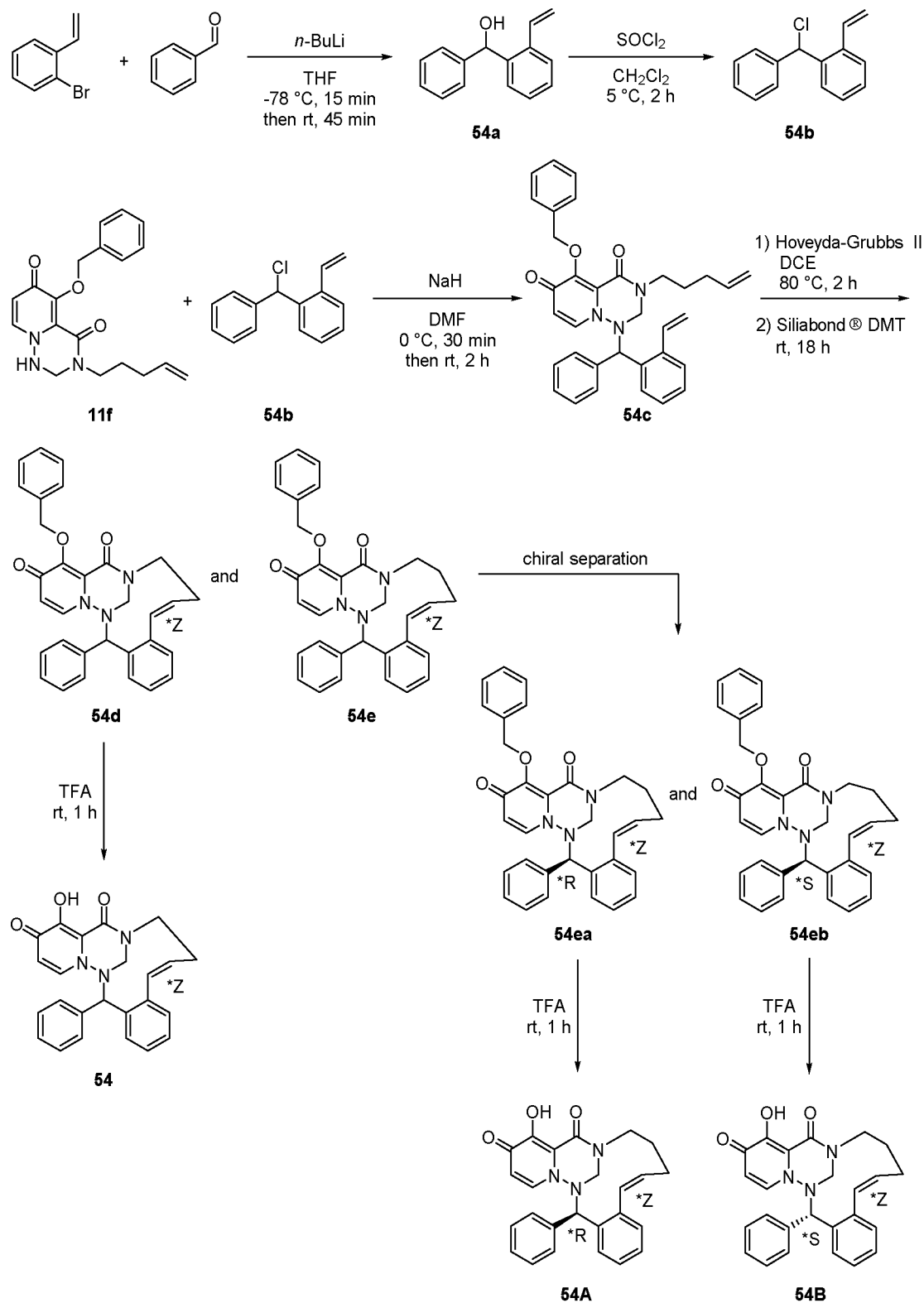
$[\alpha]_D^{20}$: +46.88° (c 0.109, DMF)

Chiral HPLC (method HPLC-B): Rt 5.52 min, chiral purity 100%

Example 54: synthesis of ($^*Z$)-4-hydroxy-15-phenyl-8,15-dihydro-7*H*-6,16-methanobenzo[*j*]pyrido[1,2-*b*][1,2,5]triazacyclododecine-3,5-dione (compound **54**), (16 $^*R,^*Z$)-4-hydroxy-16-phenyl-7,8,9,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **54A**) and (16 $^*S,^*Z$)-4-hydroxy-16-phenyl-7,8,9,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **54B**)

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**Synthesis of intermediate 54a:**

phenyl(2-vinylphenyl)methanol (intermediate **54a**, 2.9 g) was obtained using the procedure described for intermediate **23a**.

Synthesis of intermediate 54b:

1-(chloro(phenyl)methyl)-2-vinylbenzene (intermediate **54b**, 54 mg) was obtained using the procedure described for intermediate **5a**.

5 Synthesis of intermediate 54c:

5-(benzyloxy)-3-(pent-4-en-1-yl)-1-(phenyl(2-vinylphenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **54c**, 0.85 g) was obtained using the procedure described for intermediate **2d**.

10 Synthesis of intermediates 54d, 54e:

(*Z)-4-(benzyloxy)-16-phenyl-7,8,9,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **54e**) and (*Z)-4-(benzyloxy)-15-phenyl-8,15-dihydro-7*H*-6,16-methanobenzo[*j*]pyrido[1,2-

b][1,2,5]triazacyclododecine-3,5-dione (intermediate **54d**) were obtained using the procedure described for intermediate **1f**. Purification was carried out by flash chromatography over silica gel (30 μ m, 40 g, CH₂Cl₂/MeOH from 100/0 to 98/2). A second purification was performed via reverse phase (Stationary phase: YMC-actus Triart C18 10 μ m 30*150mm, Mobile phase gradient: aq. 0.2% NH₄HCO₃/CH₃CN from 55/45 to 30/70) to afford intermediate **54e** (64 mg) and intermediate **54d** (30 mg).

20 The enantiomers **54ea** and **54eb** were separated via chiral SFC (Stationary phase: Chiralpak AS-H 5 μ m 250*20mm, Mobile phase: 50% CO₂, 50% EtOH) to afford the first eluted enantiomer **54ea** (26 mg) and the second eluted enantiomer **54eb** (26 mg).

Synthesis of compound 54:

25 (*Z)-4-hydroxy-15-phenyl-8,15-dihydro-7*H*-6,16-methanobenzo[*j*]pyrido[1,2-*b*][1,2,5]triazacyclododecine-3,5-dione (compound **54**, 17 mg) was obtained using the procedure described for compound **1**.

Compound 54:

30 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.60 (br s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.32 - 7.43 (m, 2H), 7.35 (br t, *J*=7.6 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 7.21 - 7.27 (m, 3H), 7.07 (d, *J*=7.6 Hz, 1H), 6.39 (br d, *J*=11.0 Hz, 1H), 5.94 (br td, *J*=10.9, 4.1 Hz, 1H), 5.58 (s, 1H), 5.49 (d, *J*=7.6 Hz, 1H), 5.03 (d, *J*=12.9 Hz, 1H), 4.25 (d, *J*=12.9 Hz, 1H), 3.80 (br d, *J*=13.9 Hz, 1H), 2.70 (br t, *J*=12.5 Hz, 1H), 2.23 (br t, *J*=13.2 Hz, 1H), 1.84 - 2.03 (m, 2H), 1.70 - 1.81 (m, 1H).

35 LC/MS (method LC-C): Rt 2.72 min, MH⁺ 400

Synthesis of compound 54A:

(16^{*}*R*,^{*}*Z*)-4-hydroxy-16-phenyl-7,8,9,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **54A**, 17 mg) was obtained using the procedure described for compound **1**.

- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.60 (br s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.32 - 7.43 (m, 2H), 7.35 (br t, *J*=7.6 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 7.21 - 7.27 (m, 3H), 7.07 (d, *J*=7.6 Hz, 1H), 6.39 (br d, *J*=11.0 Hz, 1H), 5.94 (br td, *J*=10.9, 4.1 Hz, 1H), 5.58 (s, 1H), 5.49 (d, *J*=7.6 Hz, 1H), 5.03 (d, *J*=12.9 Hz, 1H), 4.25 (d, *J*=12.9 Hz, 1H), 3.80 (br d, *J*=13.9 Hz, 1H), 2.70 (br t, *J*=12.5 Hz, 1H), 2.23 (br t, *J*=13.2 Hz, 1H), 1.84 - 2.03 (m, 2H), 1.70 - 1.81 (m, 1H).

LC/MS (method LC-C): Rt 2.90 min, MH⁺ 414

[α]_D²⁰: +336.18 ° (c 0.105, DMF)

Chiral HPLC (method HPLC-A): Rt 5.02 min, chiral purity 100%

15 **Synthesis of compound 54B:**

(16^{*}*S*,^{*}*Z*)-4-hydroxy-16-phenyl-7,8,9,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **54B**, 15 mg) was obtained using the procedure described for compound **1**.

20 **Compound 54B:**

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.63 (br s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.33 - 7.44 (m, 2H), 7.35 (br t, *J*=7.4 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 7.20 - 7.27 (m, 3H), 7.07 (d, *J*=7.6 Hz, 1H), 6.39 (br d, *J*=11.0 Hz, 1H), 5.94 (td, *J*=10.8, 4.3 Hz, 1H), 5.58 (s, 1H), 5.49 (d, *J*=7.6 Hz, 1H), 5.03 (d, *J*=13.2 Hz, 1H), 4.25 (d, *J*=12.9 Hz, 1H), 3.80 (br d, *J*=14.2 Hz, 1H), 2.70 (br t, *J*=12.5 Hz, 1H), 2.23 (br t, *J*=12.5 Hz, 1H), 1.85 - 2.03 (m, 2H), 1.71 - 1.82 (m, 1H).

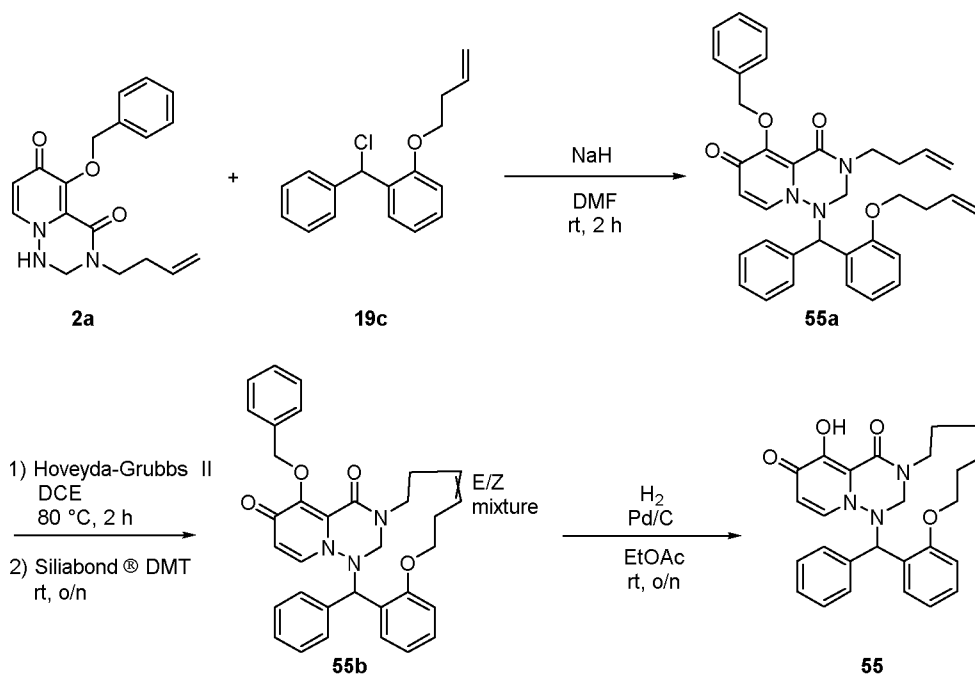
LC/MS (method LC-C): Rt 2.89 min, MH⁺ 414

[α]_D²⁰: -311.96° (c 0.092, DMF)

Chiral HPLC (method HPLC-A): Rt 6.17 min, chiral purity 100%

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Example 55: synthesis of 15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphane-14,16-dione (compound **55**)



Synthesis of intermediate **55a**:

5-(benzyloxy)-3-(but-3-en-1-yl)-1-((2-(but-3-en-1-yloxy)phenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **55a**, 3.52 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate **55b**:

(*E/Z*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (intermediate **55b**, mixture of *E* and *Z* isomers, 1.46 g) was obtained using the procedure described for intermediate **1f**.

Synthesis of compound **55**:

15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphane-14,16-dione (compound **55**, 74.7 mg) was obtained using the procedure described for compound **2**. Compound **55** was purified by flash chromatography over silica gel (30 μm, 4 g, CH₂Cl₂/CH₃OH from 99:1 to 97:3). The pure fractions were collected and evaporated to dryness. The residue was taken up in Et₂O and the solid was filtered off to give compound **55**.

Compound **55**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.60 (br s, 1H), 8.05 (dd, *J*=7.7, 1.1 Hz, 1H), 7.30 - 7.36 (m, 1H), 7.16 - 7.29 (m, 6H), 7.14 (t, *J*=7.4 Hz, 1H), 6.99 (d, *J*=8.2 Hz, 1H), 5.76 (s, 1H), 5.44 (d, *J*=7.6 Hz, 1H), 5.04 (d, *J*=13.2 Hz, 1H), 4.34 (dd, *J*=11.7, 5.4 Hz,

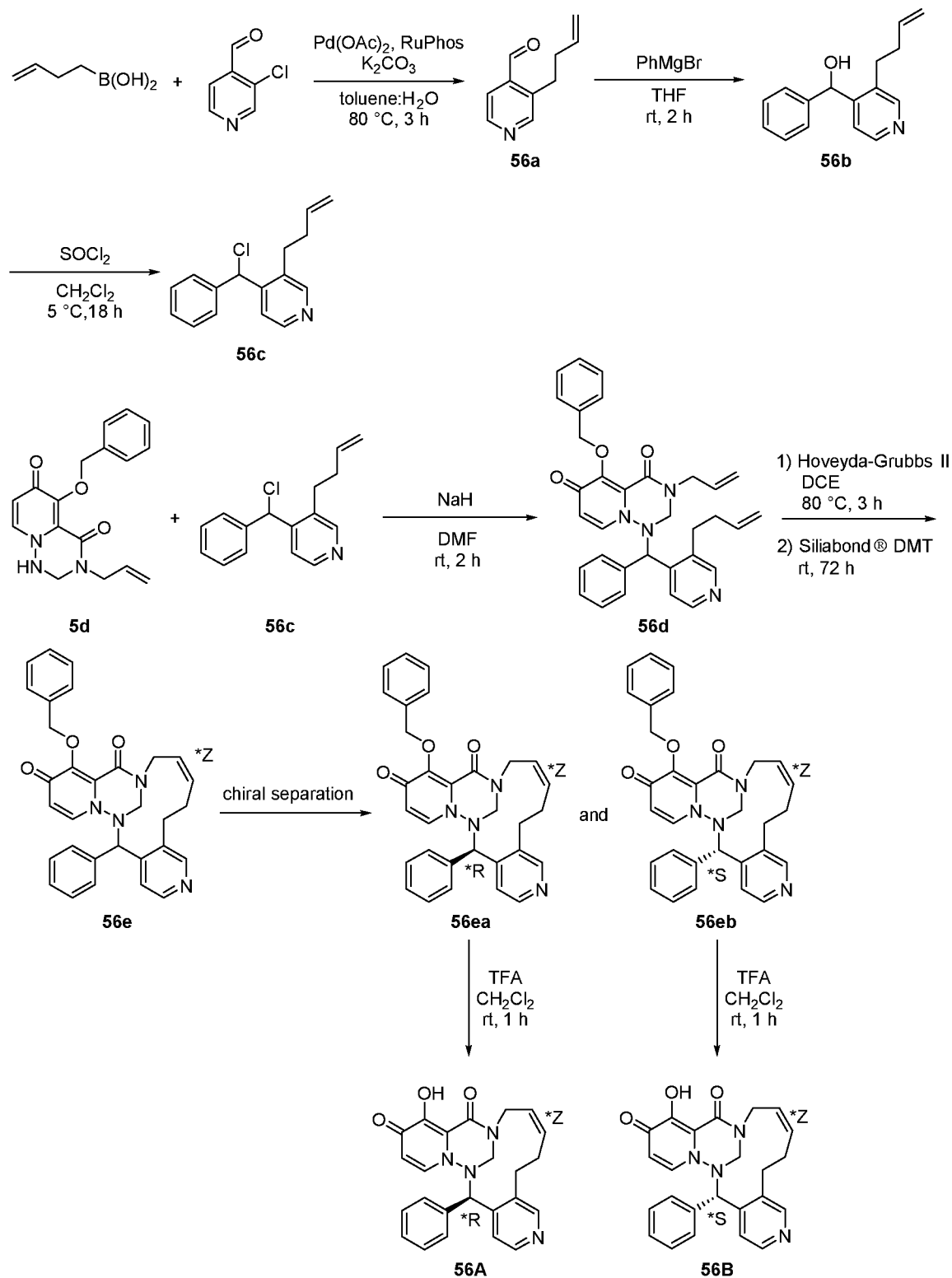
1H), 4.28 (d, $J=13.2$ Hz, 1H), 4.05 - 4.12 (m, 1H), 3.97 - 4.05 (m, 1H), 2.78 (br d, $J=13.9$ Hz, 1H), 1.77 - 1.94 (m, 3H), 1.52 - 1.65 (m, 2H), 1.42 - 1.52 (m, 1H), 1.19 - 1.32 (m, 2H).

LC/MS (method LC-C): Rt 2.95 min, MH^+ 446

5 m.p. 294.35 °C

Example 56: synthesis of (18 $^*R$, $^*Z$)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2- b :3',4'- k][1,2,5]triazacyclotridecine-11,13-dione (Compound **56A**) and (18 $^*S$, $^*Z$)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2- b :3',4'- k][1,2,5]triazacyclotridecine-11,13-dione (Compound **56B**)

10



Synthesis of intermediate 56a:

A mixture of 3-chloroisonicotinaldehyde [CAS72990-37-5] (3.00 g, 21.2 mmol), but-3-en-1-ylboronic acid (2.65 g, 26.5 mmol) and K_2CO_3 (8.79 g, 63.6 mmol) in toluene (79 mL) and water (11 mL) was degassed under nitrogen. $\text{Pd}(\text{OAc})_2$ (0.24 g, 1.06 mmol) and RuPhos (0.99 g, 2.12 mmol) were added and the reaction mixture was stirred at 80 °C

for 3 h. A 1M aqueous solution of NaOH (150 mL) was added and the mixture was extracted with EtOAc (twice). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. Purification was carried out by flash chromatography over silica gel (30 µm, 80 g, heptane/EtOAc from 85/15 to 65/35) to afford 3-(but-3-en-1-yl)isonicotinaldehyde (intermediate **56a**, 2.0 g).

Synthesis of intermediate 56b:

(3-(but-3-en-1-yl)pyridin-4-yl)(phenyl)methanol (intermediate **56b**, 2.4 g) was obtained using the procedure described for intermediate **2b**.

Synthesis of intermediate 56c:

3-(but-3-en-1-yl)-4-(chloro(phenyl)methyl)pyridine (intermediate **56c**, 2.4 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 56d:

3-allyl-5-(benzyloxy)-1-((3-(but-3-en-1-yl)pyridin-4-yl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **56d**, 3.4 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 56e:

(*Z)-12-(benzyloxy)-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:3',4'-*k*][1,2,5]triazacyclotridecine-11,13-dione (intermediate **56e**, 1.2 g) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 45% CO₂, 55% MeOH) to afford the first eluted enantiomer **56ea** (325 mg) and the second eluted enantiomer **56eb** (394 mg) containing impurities. Intermediate **56eb** was purified again via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 45% CO₂, 55% MeOH) to give pure intermediate **56eb** (316 mg).

Synthesis of compound 56A:

(18*R*,*Z)-12-(benzyloxy)-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:3',4'-*k*][1,2,5]triazacyclotridecine-11,13-dione (compound **56A**, 198 mg) was obtained using the procedure described for compound **1**.

Compound 56A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.61 (d, *J*=5.1 Hz, 1H), 8.42 (s, 1H), 8.03 (d, *J*=5.1 Hz, 1H), 7.11 - 7.30 (br s, 5H), 7.17 (d, *J*=7.6 Hz, 1H), 6.00 (br ddd, *J*=15.3, 8.7,

6.3 Hz, 1H), 5.42 - 5.55 (m, 1H), 5.46 (d, $J=7.6$ Hz, 1H), 5.11 - 5.19 (m, 2H), 4.73 (br dd, $J=14.1, 5.1$ Hz, 1H), 4.26 (d, $J=13.6$ Hz, 1H), 3.08 (br dd, $J=13.9, 7.8$ Hz, 1H), 2.65 (br d, $J=10.1$ Hz, 2H), 2.41 - 2.48 (m, 1H), 1.93 - 2.06 (m, 1H).

LC/MS (method LC-C): Rt 2.03 min, MH^+ 415

5 $[\alpha]_D^{20}$: +631.35° (c 0.114, DMF)

Chiral HPLC (method HPLC-A): Rt 5.96 min, chiral purity 100%

Synthesis of compound 56B:

TFA (4.8 mL, 62.6 mmol) was added to intermediate **56eb** (316 mg, 0.63 mmol). The mixture was stirred at rt for 1 h. The mixture was concentrated in vacuo. Purification was carried out by preparative LC (regular SiOH, 30 μ m, 12 g, CH_2Cl_2 /MeOH from 99/1 to 95/5). The residue was taken up in CH_2Cl_2 (4.0 mL) and Si-piperidine silicycle (0.56 g, 0.75 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was filtered, dried and freeze-dried in CH_3CN /water to give (18*S,*Z)-12-hydroxy-18-phenyl-5,6,9,18-tetrahydro-10,17-methanodipyrido[1,2-*b*:3',4'-*k*][1,2,5]triazacyclotridecine-11,13-dione (compound **56B**, 180 mg).

Compound 56B:

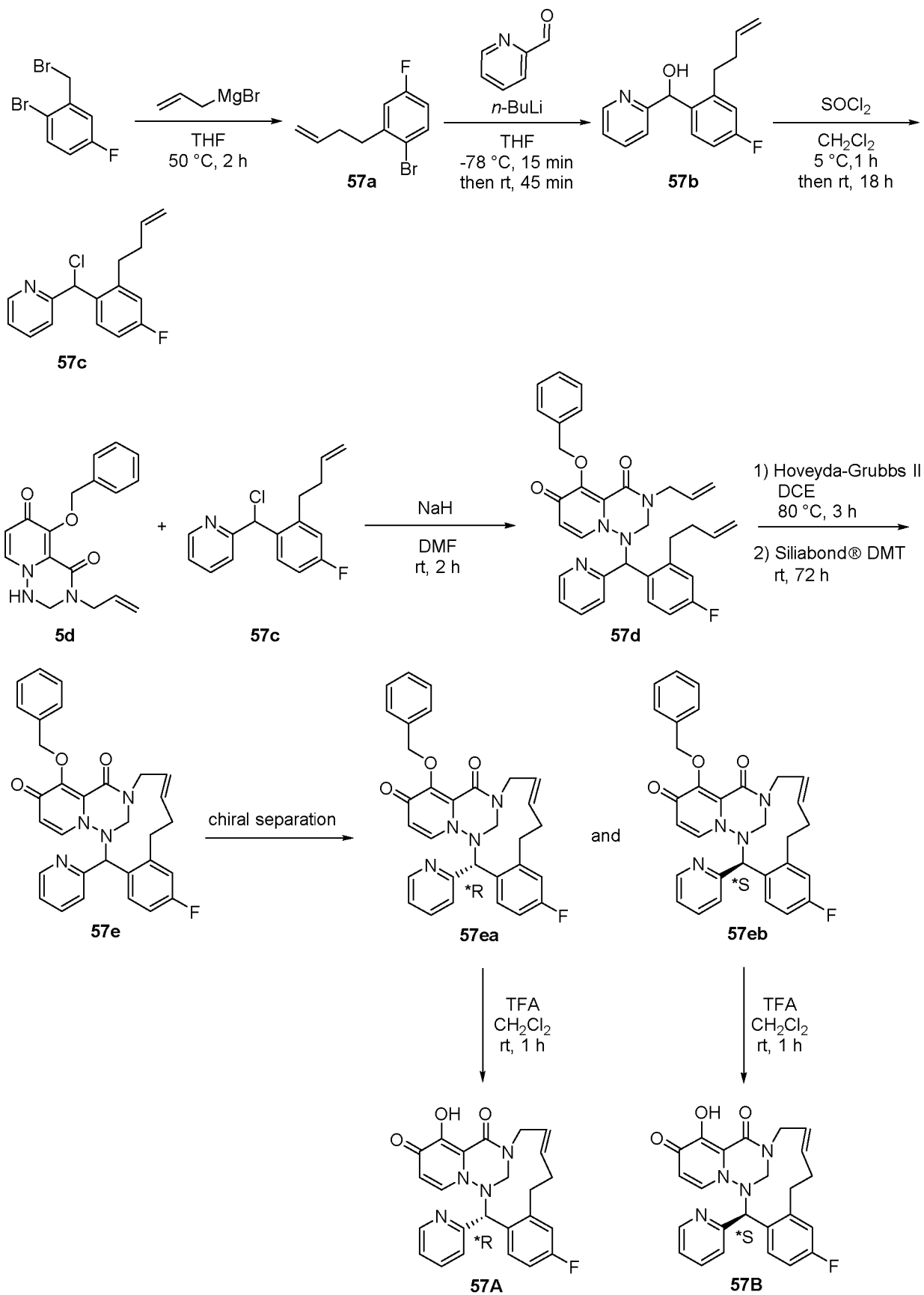
^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.62 (d, $J=5.1$ Hz, 1H), 8.42 (s, 1H), 8.03 (d, $J=5.1$ Hz, 1H), 7.09 - 7.31 (m, 6H), 5.93 - 6.06 (m, 1H), 5.42 - 5.55 (m, 1H), 5.46 (d, $J=7.6$ Hz, 1H), 5.11 - 5.20 (m, 2H), 4.73 (br dd, $J=13.6, 5.1$ Hz, 1H), 4.26 (d, $J=13.6$ Hz, 1H), 3.08 (br dd, $J=13.9, 7.8$ Hz, 1H), 2.65 (br d, $J=10.1$ Hz, 2H), 2.42 - 2.49 (m, 1H), 1.93 - 2.06 (m, 1H).

LC/MS (method LC-C): Rt 2.03 min, MH^+ 415

25 $[\alpha]_D^{20}$: -673.18° (c 0.097, DMF)

Chiral HPLC (method HPLC-A): Rt 5.40 min, chiral purity 100%

Example 57: synthesis of (16*R,E)-13-fluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **57A**) and (16*S,E)-13-fluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **57B**)



Synthesis of intermediate 57a:

Under nitrogen atmosphere, allylmagnesium bromide (1.0 M, 17 mL, 17.0 mmol) was added slowly at 0 °C to a solution of 1-bromo-2-(bromomethyl)-4-fluorobenzene [CAS 112399-50-5] (3.00 g, 11.2 mmol) in anhydrous THF (27 mL). The reaction mixture was stirred at 50 °C for 2 h. The reaction was quenched by the addition of a 10% aqueous solution of NH₄Cl and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated in vacuo to afford 1-bromo-2-(but-3-en-1-yl)-4-fluorobenzene (intermediate **57a**, 2.5 g).

Synthesis of intermediate 57b

(2-(but-3-en-1-yl)-4-fluorophenyl)(pyridin-2-yl)methanol (intermediate **57b**, 1.8 g) was obtained using the procedure described for intermediate **23a**. Crude intermediate **57b** was purified by preparative LC (Stationary phase: regular SiOH 30 µm, 40 g, Mobile phase: CH₂Cl₂/MeOH from 100/0 to 98/2).

Synthesis of intermediate 57c

2-((2-(but-3-en-1-yl)-4-fluorophenyl)chloromethyl)pyridine (intermediate **57c**, 1.9 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 57d

3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)-4-fluorophenyl)(pyridin-2-yl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **57d**, 0.90 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 57e

(*E*)-4-(benzyloxy)-13-fluoro-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **57e**, 620 mg) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 µm, 250*30 mm, Mobile phase: 60% CO₂, 40% EtOH) to afford the first eluted enantiomer **57ea** (287 mg) and the second eluted enantiomer **57eb** (298 mg).

Synthesis of compound 57A:

(16**R,E*)-13-fluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **57A**, 190 mg) was obtained using the procedure described for compound **1**.

Compound 57A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.37 (br d, *J*=4.1 Hz, 1H), 8.16 (dd, *J*=8.7, 6.1 Hz, 1H), 7.66 (td, *J*=7.7, 1.6 Hz, 1H), 7.40 (d, *J*=7.9 Hz, 1H), 7.27 (td, *J*=8.5, 2.8 Hz, 1H), 7.22 (dd, *J*=6.8, 4.9 Hz, 1H), 7.16 (d, *J*=7.9 Hz, 1H), 7.10 (dd, *J*=10.1, 2.5 Hz, 1H),
5 5.94 (br dt, *J*=15.2, 7.7 Hz, 1H), 5.50 - 5.59 (m, 1H), 5.52 (d, *J*=7.6 Hz, 1H), 5.37 (s, 1H), 5.14 (d, *J*=13.9 Hz, 1H), 4.71 (br dd, *J*=13.9, 5.0 Hz, 1H), 4.30 (d, *J*=13.6 Hz, 1H), 3.11 (dd, *J*=14.0, 8.0 Hz, 1H), 2.56 - 2.67 (m, 3H), 2.01 - 2.14 (m, 1H).

LC/MS (method LC-C): Rt 2.47 min, MH⁺ 433

[α]_D²⁰: -658.94° (c 0.104, DMF)

10 Chiral HPLC (method HPLC-A): Rt 4.97 min, chiral purity 100%

Synthesis of compound 57B:

(16**S,E*)-13-fluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **57B**,
15 187 mg) was obtained using the procedure described for compound **1**.

Compound 57B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.36 (d, *J*=4.1 Hz, 1H), 8.15 (dd, *J*=8.8, 6.3 Hz, 1H), 7.65 (td, *J*=7.7, 1.6 Hz, 1H), 7.40 (d, *J*=7.9 Hz, 1H), 7.27 (td, *J*=8.6, 2.7 Hz, 1H),
20 7.22 (dd, *J*=6.9, 5.0 Hz, 1H), 7.15 (d, *J*=7.6 Hz, 1H), 7.10 (dd, *J*=10.1, 2.8 Hz, 1H), 5.94 (dt, *J*=15.4, 7.7 Hz, 1H), 5.49 - 5.58 (m, 1H), 5.51 (d, *J*=7.6 Hz, 1H), 5.37 (s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.71 (dd, *J*=14.0, 4.9 Hz, 1H), 4.29 (d, *J*=13.9 Hz, 1H), 3.10 (dd, *J*=13.9, 8.2 Hz, 1H), 2.54 - 2.66 (m, 3H), 2.02 - 2.13 (m, 1H).

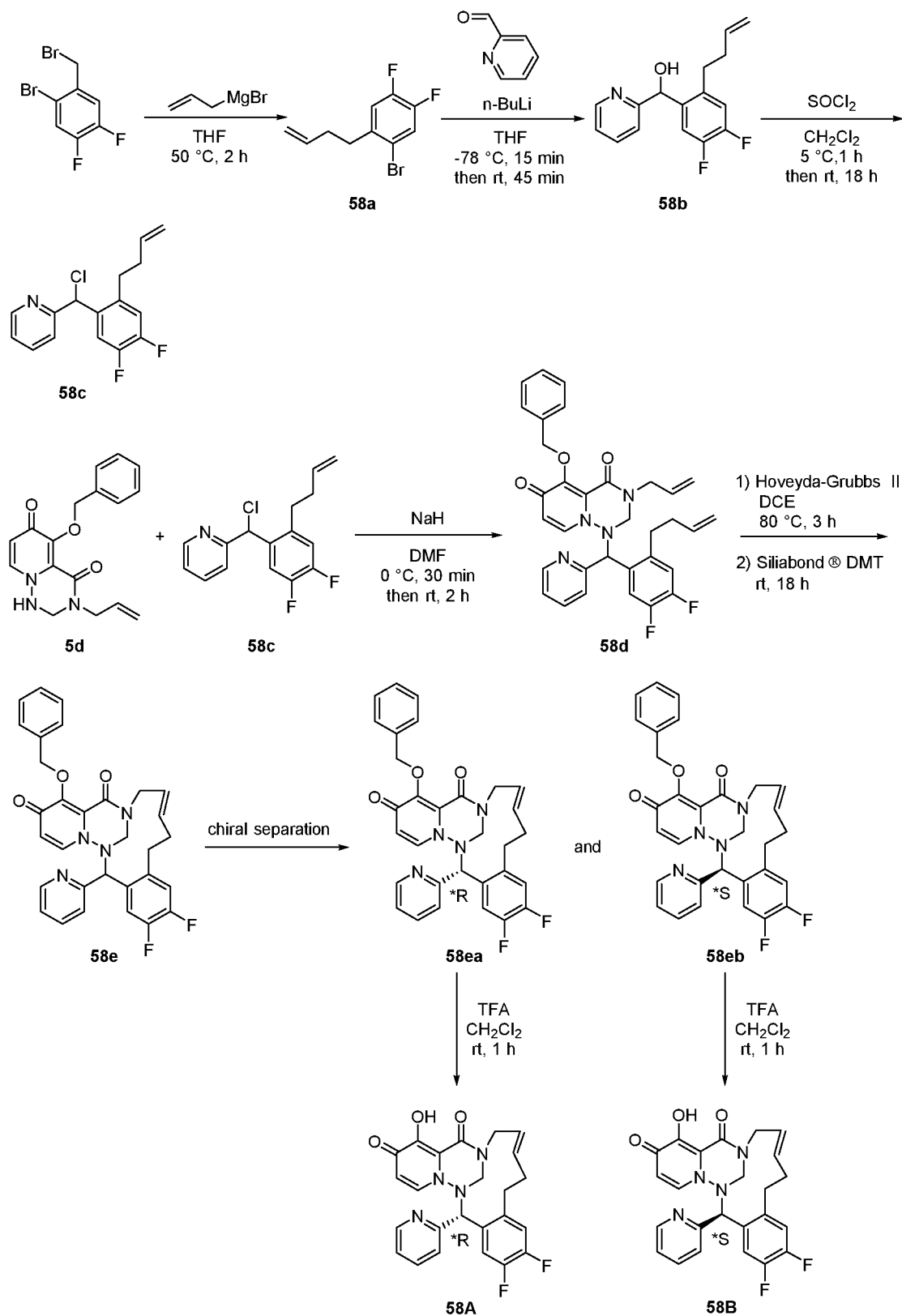
LC/MS (method LC-C): Rt 2.47 min, MH⁺ 433

25 [α]_D²⁰: +588.55° (c 0.131, DMF)

Chiral HPLC (method HPLC-A): Rt 5.64 min, chiral purity 100%

Example 58: synthesis of (16**R,E*)-13,14-difluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **58A**) and (16**S,E*)-13,14-difluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **58B**)
30

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Synthesis of intermediate 58a:

1-Bromo-2-(but-3-en-1-yl)-4,5-difluorobenzene (intermediate **58a**, 2.5 g) was obtained using the procedure described for intermediate **57a**.

Synthesis of intermediate 58b

(2-(But-3-en-1-yl)-4,5-difluorophenyl)(pyridin-2-yl)methanol (intermediate **58b**, 0.72 g) was obtained using the procedure described for intermediate **23a**.

5 Synthesis of intermediate 58c

2-((2-(But-3-en-1-yl)-4,5-difluorophenyl)chloromethyl)pyridine (intermediate **58c**, 770 mg) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 58d

10 3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)-4,5-difluorophenyl)(pyridin-2-yl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **58d**, 0.71 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 58e

15 (*E*)-4-(benzyloxy)-13,14-difluoro-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **58e**, 0.57 g) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 μ m, 250*30 mm, Mobile phase: 60% CO₂, 40% EtOH) to afford the first eluted
20 enantiomer **58ea** (234 mg) and the second eluted enantiomer **58eb** (228 mg).

Synthesis of compound 58A:

(16**R,E*)-13,14-difluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **58A**,
25 145 mg) was obtained using the procedure described for compound **1**.

Compound 58A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.39 (d, *J*=4.1 Hz, 1H), 8.12 (dd, *J*=12.6, 8.5 Hz, 1H), 7.67 (td, *J*=7.7, 1.6 Hz, 1H), 7.45 (d, *J*=7.9 Hz, 2H), 7.35 (dd, *J*=11.8, 8.4 Hz, 1H),
30 7.24 (dd, *J*=7.1, 5.2 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H), 5.94 (dt, *J*=15.4, 7.6 Hz, 1H), 5.54 - 5.64 (m, 1H), 5.50 (d, *J*=7.9 Hz, 1H), 5.35 (s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.71 (br dd, *J*=13.9, 5.0 Hz, 1H), 4.35 (d, *J*=13.6 Hz, 1H), 3.09 (dd, *J*=13.9, 8.2 Hz, 1H), 2.53 - 2.63 (m, 3H), 2.01 - 2.13 (m, 1H).

LC/MS (method LC-C): Rt 2.59 min, MH⁺ 451

35 $[\alpha]_D^{20}$: -602.11° (c 0.161, DMF)

Chiral HPLC (method HPLC-A): Rt 4.47 min, chiral purity 100%

Synthesis of compound 58B:

(16*S,*E*)-13,14-difluoro-4-hydroxy-16-(pyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **58B**, 145 mg) was obtained using the procedure described for compound **1**.

5

Compound 58B:

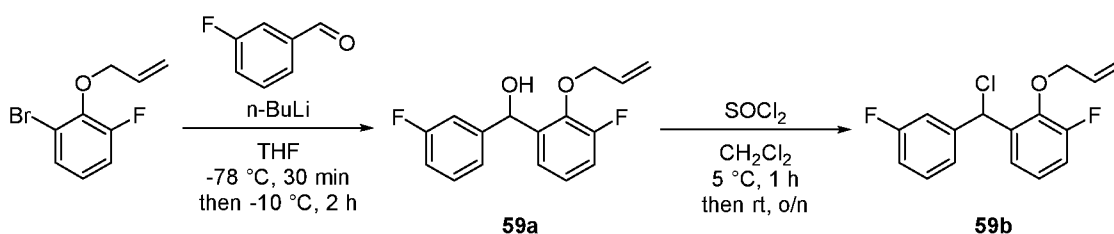
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.39 (br d, *J*=4.4 Hz, 1H), 8.12 (dd, *J*=12.3, 8.5 Hz, 1H), 7.67 (br td, *J*=7.6, 1.4 Hz, 1H), 7.42 - 7.48 (m, 2H), 7.35 (br dd, *J*=11.7, 8.5 Hz, 1H), 7.24 (dd, *J*=6.9, 5.0 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H), 5.94 (dt, *J*=15.3, 7.5 Hz, 1H), 5.55 - 5.64 (m, 1H), 5.51 (d, *J*=7.9 Hz, 1H), 5.35 (s, 1H), 5.13 (d, *J*=13.9 Hz, 1H), 4.71 (br dd, *J*=13.9, 5.0 Hz, 1H), 4.35 (d, *J*=13.9 Hz, 1H), 3.09 (br dd, *J*=13.9, 8.2 Hz, 1H), 2.53 - 2.63 (m, 3H), 2.02 - 2.13 (m, 1H).

LC/MS (method LC-C): Rt 2.59 min, MH⁺ 451

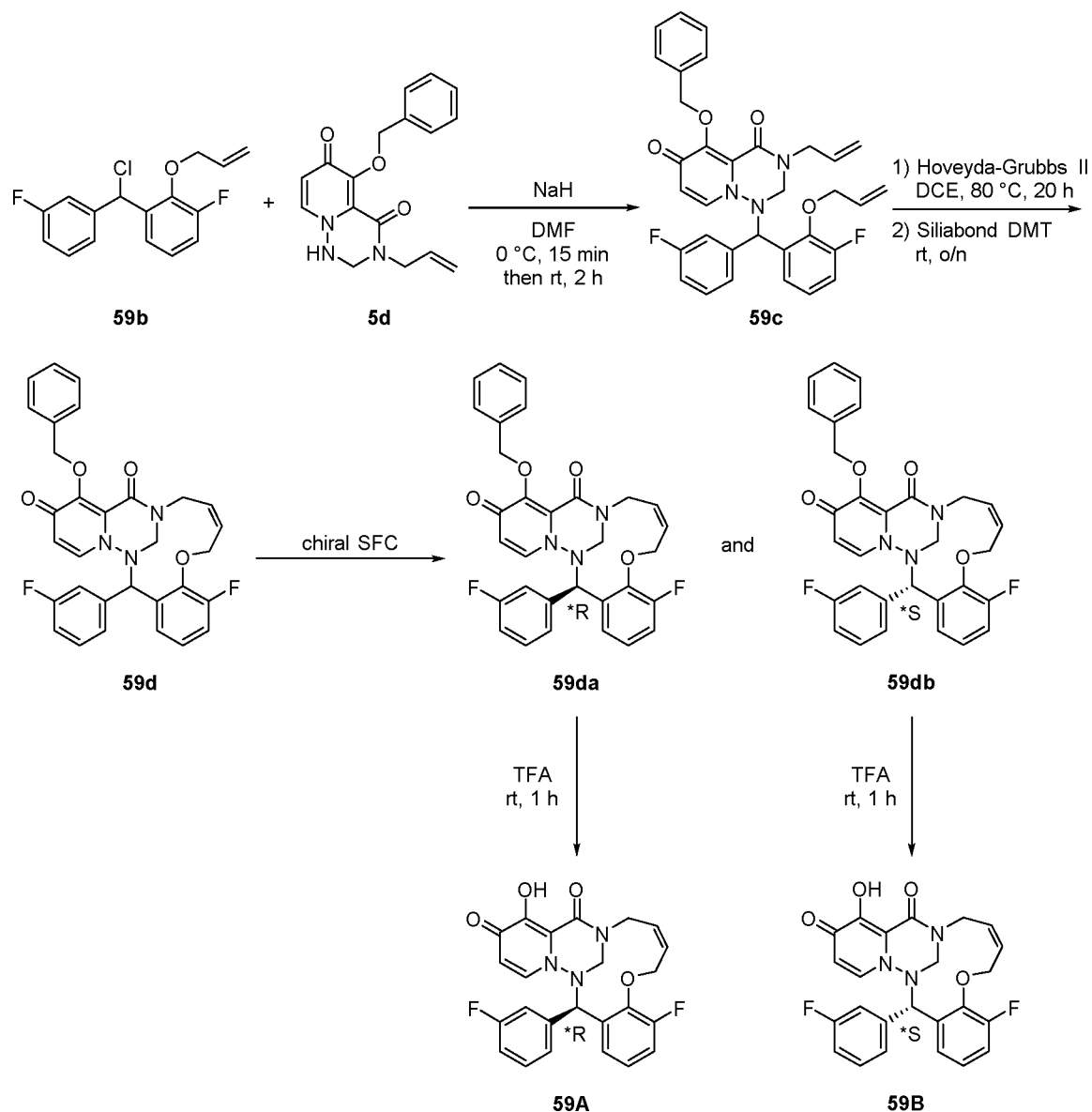
[α]_D²⁰: +618.82° (c 0.085, DMF)

15 Chiral HPLC (method HPLC-A): Rt 5.16 min, chiral purity 100%

Example 59: synthesis of (18*R,*Z*)-4-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **59A**) and (18*S,*Z*)-4-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **59B**)



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**Synthesis of intermediate 59a:**

2-(allyloxy)-1-bromo-3-fluorobenzene [CAS 1010422-27-1] (5.00 g, 21.6 mmol) was dissolved in anhydrous THF (50 mL). The reaction mixture was cooled to -78 °C and *n*-BuLi (2.5 M, 9.1 mL, 22.7 mmol) was added dropwise. After 15 min 3-fluorobenzaldehyde (2.82 g, 22.7 mmol) was added. The reaction mixture was stirred at -78 °C for 45 min and slowly warmed to -10 °C over 2 h. The reaction was quenched by addition of a saturated aqueous of NH₄Cl (50 mL). The aqueous phase was extracted with EtOAc (twice). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash chromatography (80 g, petroleum ether/EtOAc from 100/0 to 85/15) to afford (2-(allyloxy)-3-fluorophenyl)(3-fluorophenyl)methanol (intermediate **59a**, 3.2 g).

Synthesis of intermediate 59b

2-(allyloxy)-1-(chloro(3-fluorophenyl)methyl)-3-fluorobenzene ene (intermediate **59b**, 3.4 g) was obtained using the procedure described for intermediate **5a**.

5 Synthesis of intermediate 59c

3-allyl-1-((2-(allyloxy)-3-fluorophenyl)(3-fluorophenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **59c**, 960 mg) was obtained using the procedure reported for intermediate **2d**.

10 Synthesis of intermediate 59d

A degassed solution of intermediate **59c** (1.00 g, 1.76 mmol) and Hoveyda-Grubbs second generation catalyst (220 mg, 0.35mmol) in anhydrous DCE (90 mL) was stirred at 80 °C for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (120 g, CH₂Cl₂/MeOH from 100/0 to 98/2). The residue was dissolved in CH₂Cl₂ (60 mL) and siliabond DMT (4.61 g, 0.28 mmol) was added. The mixture was stirred at rt overnight. The reaction mixture was filtered through Celite®. The filter-cake was washed with CH₂Cl₂ and the filtrate was evaporated under reduced pressure. Purification was carried out by flash chromatography (80 g, CH₂Cl₂/MeOH from 100/0 to 98/2). A second purification was performed by flash chromatography C18 (45 g, H₂O/MeOH from 70/30 to 0/100). The residue was purified a last time by flash chromatography (40 g, CH₂Cl₂/MeOH from 100/0 to 98/2) to afford (Z)-12-(benzyloxy)-4-fluoro-18-(3-fluorophenyl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **59d**, 130 mg).

The enantiomers were separated by chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250*30mm, Mobile phase: 65% CO₂, 35% EtOH) to give the first eluted enantiomer **59da** (39 mg) and the second eluted enantiomer **59db** (46 mg).

Synthesis of compound 59A:

(18**R,Z*)-4-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **59A**, 25 mg) was obtained using the procedure described for compound **1**.

Compound 59A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (br d, *J*=7.6 Hz, 1H), 7.32 - 7.45 (m, 3H), 7.20 - 7.28 (m, 1H), 7.04 - 7.15 (m, 2H), 7.00 (br s, 1H), 6.26 (br s, 1H), 5.95 (br s, 1H), 5.56 (d, *J*=7.6 Hz, 1H), 5.31 (br s, 1H), 5.15 (d, *J*=13.9 Hz, 1H), 4.81 (br dd, *J*=13.4, 4.3 Hz, 2H), 4.26 (d, *J*=13.9 Hz, 1H), 4.21 (br s, 1H), 3.20 (br dd, *J*=13.9, 7.9 Hz, 1H).

LC/MS (method LC-C): Rt 2.63 min, MH^+ 452

$[\alpha]_D^{20}$: -667.62 ° (c 0.104, DMF)

Chiral HPLC (method HPLC-B): Rt 5.90 min, chiral purity 100%

5 **Synthesis of compound 59B:**

(18^{*}*S,Z*)-4-fluoro-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **59B**, 28 mg) was obtained using the procedure described for compound **1**.

10 **Compound 59B:**

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (br d, *J*=7.6 Hz, 1H), 7.32 - 7.45 (m, 3H), 7.19 - 7.28 (m, 1H), 7.03 - 7.14 (m, 2H), 7.00 (br s, 1H), 6.26 (br s, 1H), 5.94 (br s, 1H), 5.57 (d, *J*=7.6 Hz, 1H), 5.31 (br s, 1H), 5.15 (d, *J*=13.9 Hz, 1H), 4.81 (br dd, *J*=13.6, 4.4 Hz, 2H), 4.26 (d, *J*=13.9 Hz, 1H), 4.20 (br s, 1H), 3.21 (br dd, *J*=13.9, 7.9 Hz, 1H).

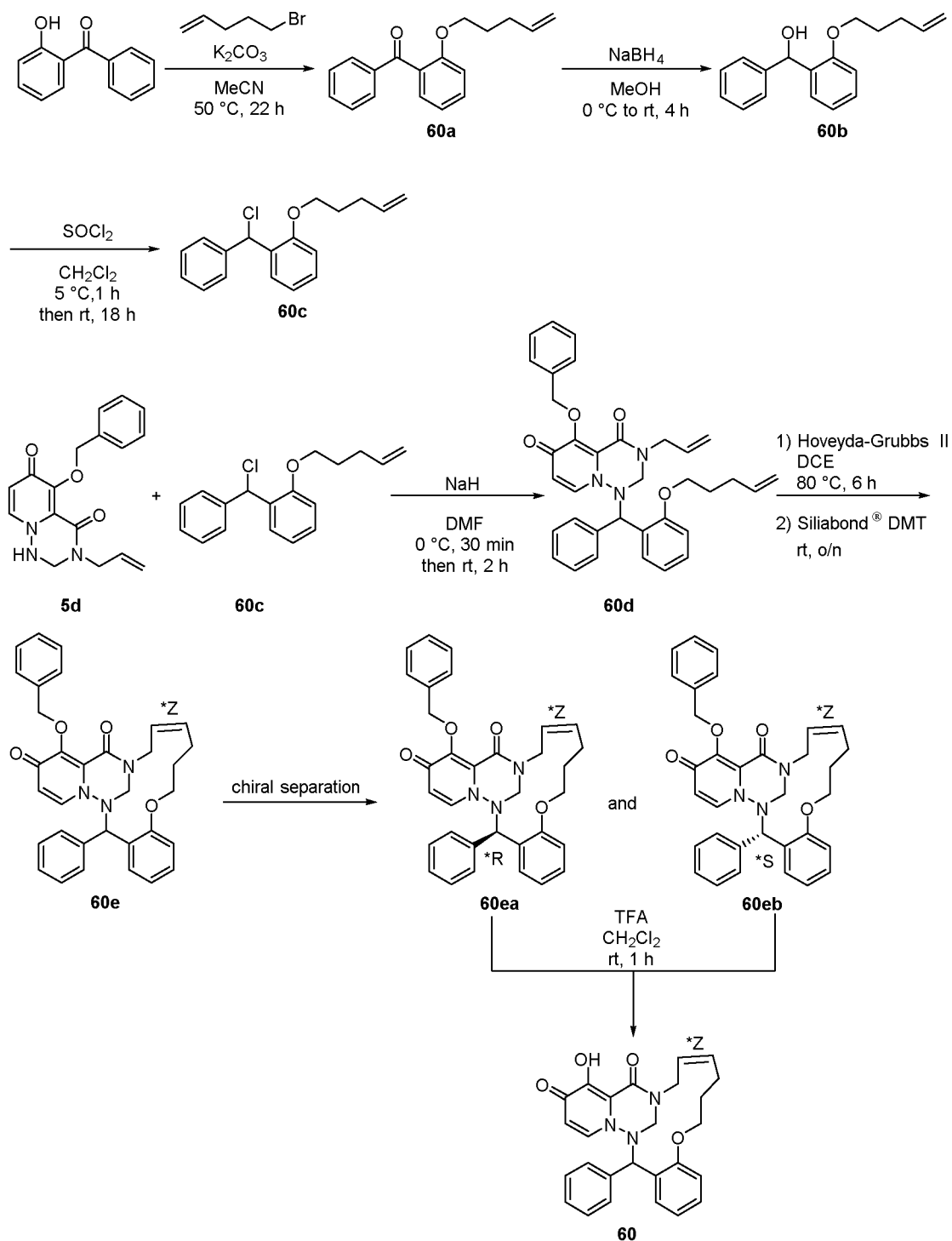
15 LC/MS (method LC-C): Rt 2.63 min, MH^+ 452

$[\alpha]_D^{20}$: +592.34 ° (c 0.102, DMF)

Chiral HPLC (method HPLC-B): Rt 4.56 min, chiral purity 100%

Example 60: synthesis of (**Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-8-ene-14,16-dione (Compound **60**)

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**Synthesis of intermediate 60a:**

(2-(pent-4-en-1-yloxy)phenyl)(phenyl)methanone (intermediate **60a**, 6.91 g) was obtained using the procedure described for intermediate **19a**.

5

Synthesis of intermediate 60b:

(2-(pent-4-en-1-yloxy)phenyl)(phenyl)methanol (intermediate **60b**, 7.71 g) was obtained using the procedure described for intermediate **11b**.

Synthesis of intermediate 60c:

1-(chloro(phenyl)methyl)-2-(pent-4-en-1-yloxy)benzene (intermediate **60c**, 3.5 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 60d:

3-allyl-5-(benzyloxy)-1-((2-(pent-4-en-1-yloxy)phenyl)(phenyl)methyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **60d**, 2.0 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 60e:

(*Z)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-8-ene-14,16-dione (intermediate **60e**, 872 mg) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: Welk-O1 (S,S) 5 μ m 250*21.2mm, Mobile phase: 50% CO₂, 50% MeOH) to afford the first eluted enantiomer **60ea** (414 mg) and the second eluted enantiomer **60eb** (389 mg).

Synthesis of compound 60:

(*Z)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-8-ene-14,16-dione (compound **60**, 120 mg) was obtained using the procedure described for compound **1**. Racemization occurred during the reaction leading to the synthesis of racemic compound **60**. Racemization was also observed when starting from enantiomer **60eb**.

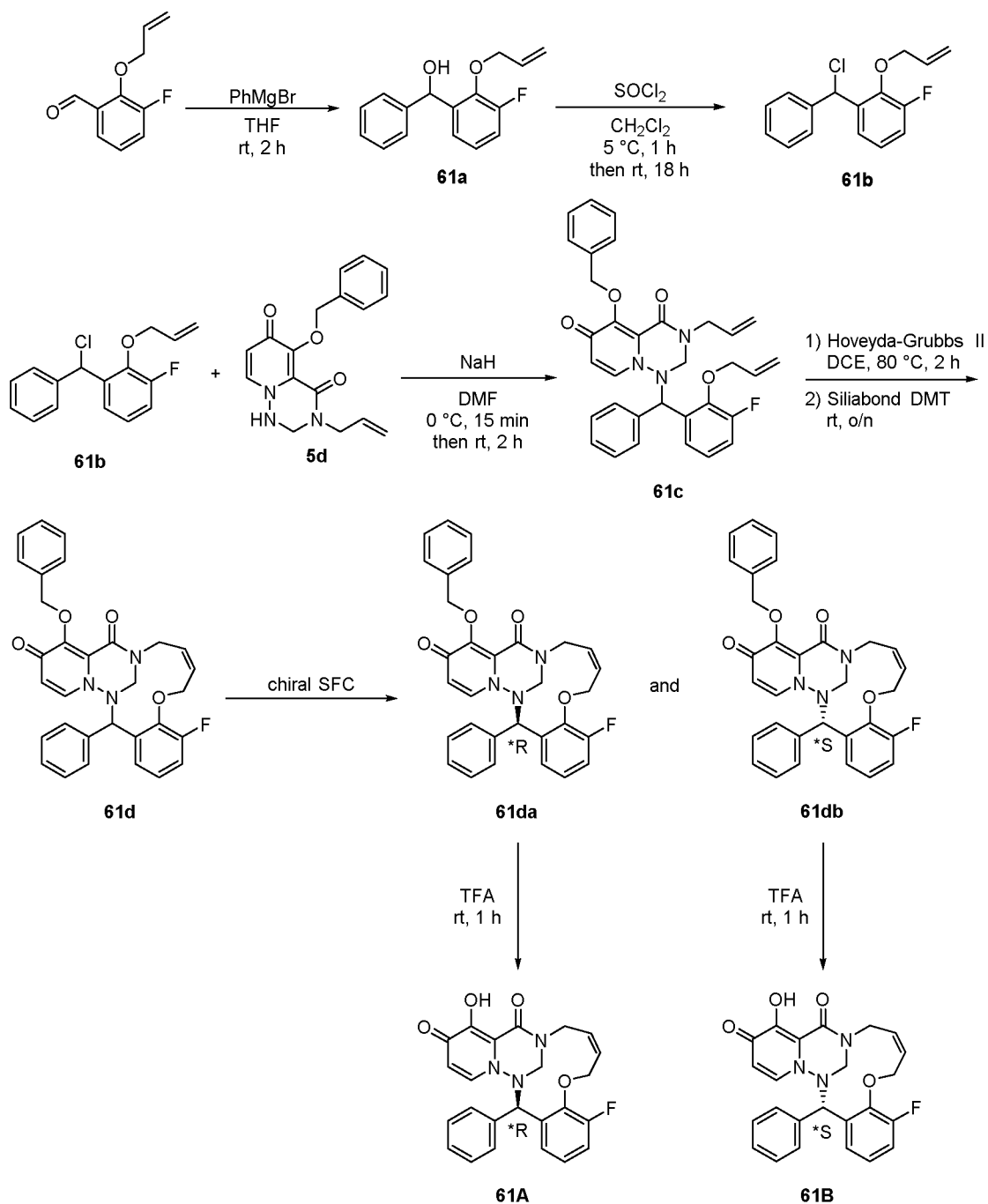
Compound 60:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.40 (br s, 1H), 8.09 (br d, *J*=6.9 Hz, 1H), 7.28 - 7.36 (m, 2H), 7.18 (br s, 5H), 7.11 (br t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=8.2 Hz, 1H), 5.82 - 5.89 (m, 1H), 5.81 (s, 1H), 5.54 (br dd, *J*=16.2, 4.6 Hz, 1H), 5.46 (d, *J*=7.6 Hz, 1H), 5.12 (d, *J*=13.2 Hz, 1H), 4.42 (br d, *J*=15.8 Hz, 1H), 4.21 (d, *J*=12.9 Hz, 1H), 4.02 - 4.16 (m, 1H), 3.24 (br dd, *J*=15.6, 7.1 Hz, 2H), 2.38 - 2.45 (m, 2H), 2.18 - 2.29 (m, 1H), 1.89 - 1.98 (m, 1H), 1.74 - 1.84 (m, 1H).

LC/MS (method LC-C): Rt 2.84 min, MH⁺ 444

Example 61: synthesis of (18*R,Z)-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **61A**) and (18*S,Z)-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-

10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **61B**)



5

Synthesis of intermediate 61a:

(2-(allyloxy)-3-fluorophenyl)(phenyl)methanol (intermediate **61a**, 2.8 g) was obtained using the procedure described for intermediate **2b**. Crude intermediate **61a** was purified by flash chromatography over silica gel (30 μm , 80 g, heptane/EtOAc 90/10).

10

Synthesis of intermediate 61b

2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene (intermediate **61b**, 3.0 g) was obtained using the procedure described for intermediate **5a**.

5 Synthesis of intermediate 61c

3-allyl-1-((2-(allyloxy)-3-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **61c**, 0.65 g) was obtained using the procedure described for intermediate **2d**.

10 Synthesis of intermediate 61d

(Z)-12-(benzyloxy)-4-fluoro-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **61d**, 0.50 g) was obtained using the procedure described for intermediate **1f**.

15 The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK IC 5 μ m 250*30mm, Mobile phase: 40% CO₂, 60% (MeOH/CH₂Cl₂ 90/10) to afford the first eluted enantiomer **61da** (250 mg) and the second eluted enantiomer **61db** (250 mg).

Synthesis of compound 61A:

20 (18**R,Z*)-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **61A**, 90 mg) was obtained using the procedure described for compound **1**.

Compound 61A:

25 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.91 (br d, *J*=7.6 Hz, 1H), 7.30 - 7.45 (m, 2H), 7.03 - 7.25 (m, 6H), 6.22 (br s, 1H), 5.94 (br s, 1H), 5.48 (d, *J*=8.1 Hz, 1H), 5.28 (s, 1H), 5.14 (d, *J*=13.6 Hz, 1H), 4.70 - 4.86 (m, 2H), 4.27 (d, *J*=13.6 Hz, 1H), 4.21 (br s, 1H), 3.21 (br dd, *J*=13.9, 7.8 Hz, 1H).

LC/MS (method LC-C): Rt 2.58 min, MH⁺ 434

30 [α]_D²⁰: -676.19 ° (c 0.157, DMF)

Chiral HPLC (method HPLC-B): Rt 7.89 min, chiral purity 99.25%

Synthesis of compound 61B:

35 (18**S,Z*)-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **61B**, 105 mg) was obtained using the procedure described for compound **1**.

Compound 61B:

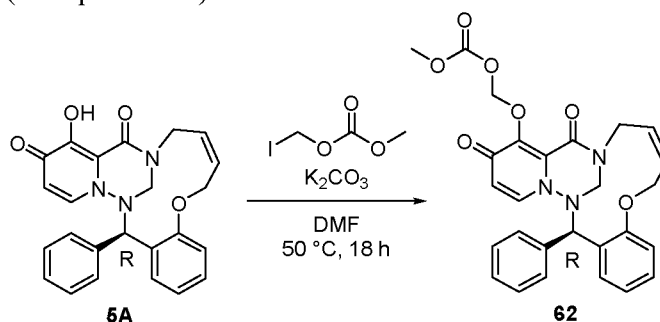
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.91 (br d, *J*=7.6 Hz, 1H), 7.31 - 7.44 (m, 2H), 7.05 - 7.26 (m, 6H), 6.22 (br s, 1H), 5.94 (br s, 1H), 5.48 (d, *J*=7.6 Hz, 1H), 5.28 (s, 1H), 5.14 (d, *J*=13.6 Hz, 1H), 4.74 - 4.86 (m, 2H), 4.27 (d, *J*=14.1 Hz, 1H), 4.21 (br s, 1H), 3.21 (br dd, *J*=13.9, 7.8 Hz, 1H).

LC/MS (method LC-C): Rt 2.57 min, MH⁺ 434

[α]_D²⁰: +671.76 ° (c 0.131, DMF)

Chiral HPLC (method HPLC-B): Rt 6.10 min, chiral purity 100%

- 10 **Example 62:** synthesis of (((18*R,Z*)-11,13-dioxo-18-phenyl-6,9,11,13-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecin-12-yl)oxy)methyl methyl carbonate (Compound **62**)



- 15 Iodomethyl methyl carbonate [69862-08-4] (200 mg, 0.94 mmol) was added dropwise to a suspension of compound **5A** (260 mg, 0.63 mmol) and K₂CO₃ (173 mg, 1.25 mmol) in DMF (4.8 mL). The reaction mixture was stirred at 50 °C for 18 h. The reaction mixture was diluted with water and EtOAc. The organic phase was washed with brine (5 times), dried over MgSO₄, filtered and evaporated in vacuo. Purification was carried out by flash chromatography over silica gel (30 μm, 12 g, CH₂Cl₂/CH₃OH from 100/0 to 98/2). The residue was freeze-dried (CH₃CN/water) to give (((18*R,Z*)-11,13-dioxo-18-phenyl-6,9,11,13-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecin-12-yl)oxy)methyl methyl carbonate (compound **62**, 130 mg).

Compound 62:

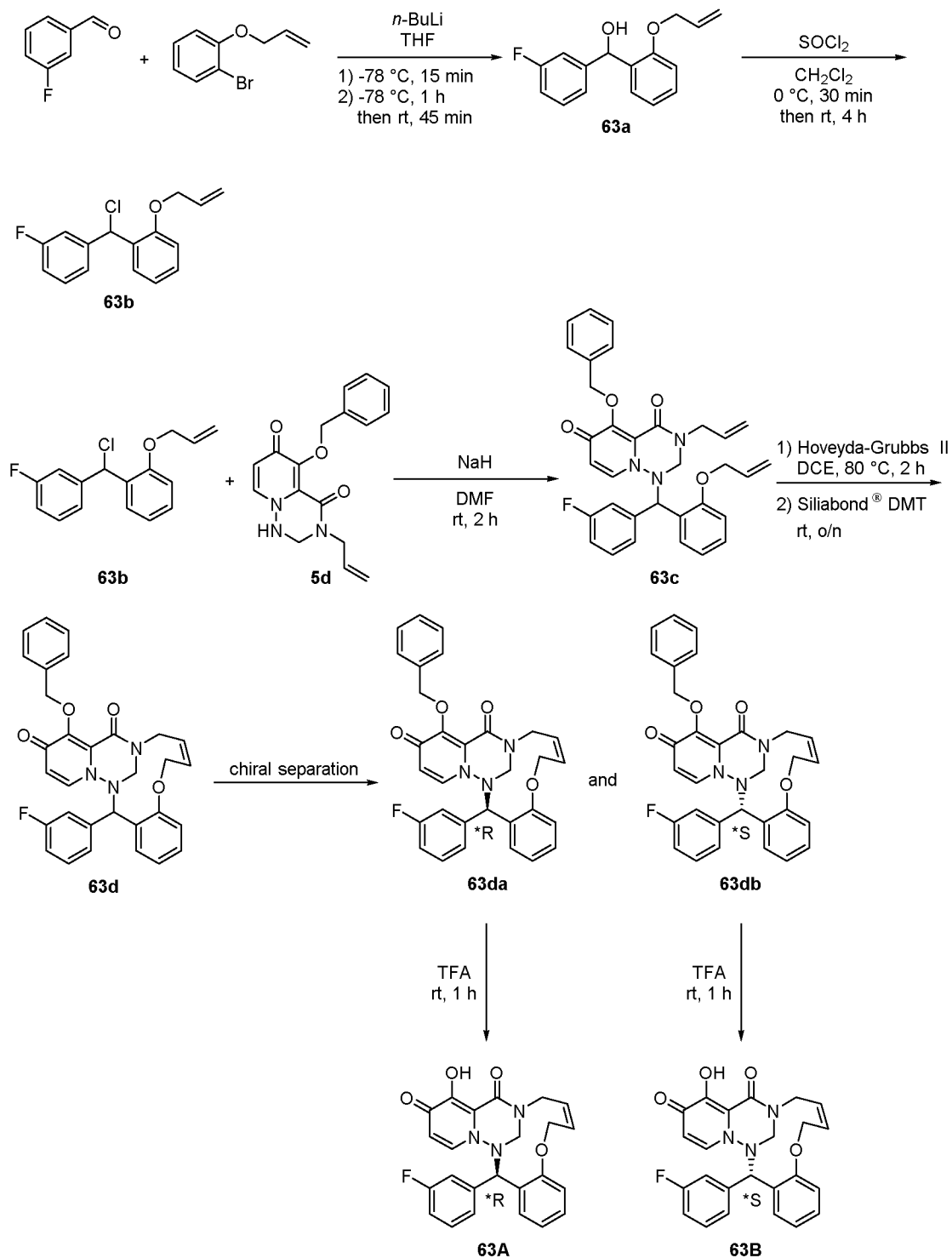
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 (br d, *J*=7.6 Hz, 1 H), 7.40 - 7.46 (m, 1H), 7.35 (br t, *J*=7.4 Hz, 1H), 7.30 (d, *J*=7.6 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 1H), 7.16 - 7.21 (m, 3H), 7.04 - 7.16 (m, 2H), 6.05 - 6.16 (m, 1H), 5.91 (br s, 1H), 5.74 (d, *J*=6.1 Hz, 1H), 5.68 (d, *J*=8.1 Hz, 1H), 5.54 (d, *J*=6.6 Hz, 1H), 5.30 (s, 1H), 5.08 (d, *J*=13.6 Hz, 1H), 4.63 - 4.78 (m, 2H), 4.27 - 4.35 (m, 1H), 4.19 (d, *J*=14.1 Hz, 1H), 3.78 (s, 3H), 3.16 (dd, *J*=13.6, 8.6 Hz, 1H).

LC/MS (method LC-A): Rt 2.52 min, MH⁺ 504

[α]_D²⁰: -625.81° (c 0.155, DMF)

Example 63: synthesis of (18**R,Z*)-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-
5 10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **63A**) and (18**S,Z*)-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-
10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **63B**)

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**Synthesis of intermediate 63a:**

(2-(allyloxy)phenyl)(3-fluorophenyl)methanol (intermediate **63a**, 2.64 g) was obtained using the procedure described for intermediate **23a**.

5

Synthesis of intermediate 63b:

1-(allyloxy)-2-(chloro(3-fluorophenyl)methyl)benzene (intermediate **63b**, 3.00 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 63c:

3-allyl-1-((2-(allyloxy)phenyl)(3-fluorophenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **63c**, 3.3 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 63d:

(*Z*)-12-(benzyloxy)-18-(3-fluorophenyl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **63d**, 560 mg) was obtained using the procedure described for intermediate **1f**. Crude intermediate **63d** was purified by flash chromatography over silica gel (15-40 μ m, 40 g, CH₂Cl₂/CH₃OH from 100/0 to 97/3). A second purification was performed via preparative LC (Stationary phase: irregular bare silica 40 g, Mobile phase: heptane/CH₃OH/EtOAc 42/8/50).

The enantiomers were separated by chiral SFC (Stationary phase: CHIRACEL OJ-H 5 μ m 250*30mm, Mobile phase: 80% CO₂, 20% MeOH) to afford the first eluted enantiomer **63da** (242 mg) and the second eluted enantiomer **63db** (232 mg).

Synthesis of compound 63A

(18**R,Z*)-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **63A**, 73 mg) was obtained using the procedure described for compound **1**. After purification by flash chromatography, compound **63A** was crystallized from CH₃CN and Et₂O.

Compound 63A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.96 (br s, 1H), 8.10 (br d, *J*=7.6 Hz, 1H), 7.40 - 7.46 (m, 1H), 7.32 - 7.39 (m, 2H), 7.19 - 7.26 (m, 2H), 6.90 - 7.12 (m, 3H), 6.09 - 6.21 (m, 1H), 5.88 (br s, 1H), 5.56 (d, *J*=7.6 Hz, 1H), 5.34 (s, 1H), 5.11 (d, *J*=13.9 Hz, 1H), 4.70 - 4.82 (m, 2H), 4.25 - 4.35 (m, 1H), 4.22 (d, *J*=13.6 Hz, 1H), 3.19 (br dd, *J*=13.7, 8.4 Hz, 1H).

LC/MS (method LC-C): Rt 2.55 min, MH⁺ 434

[α]_D²⁰: +660.6° (c 0.214, DMF)

Chiral HPLC (method HPLC-B): Rt 5.07 min, chiral purity 100%

Synthesis of compound 63B:

(18**S,Z*)-18-(3-fluorophenyl)-12-hydroxy-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound

63B, 70 mg) was obtained using the procedure described for compound **1**. After purification by flash chromatography, compound **63B** was crystallized from CH₃CN and Et₂O.

5 **Compound 63B:**

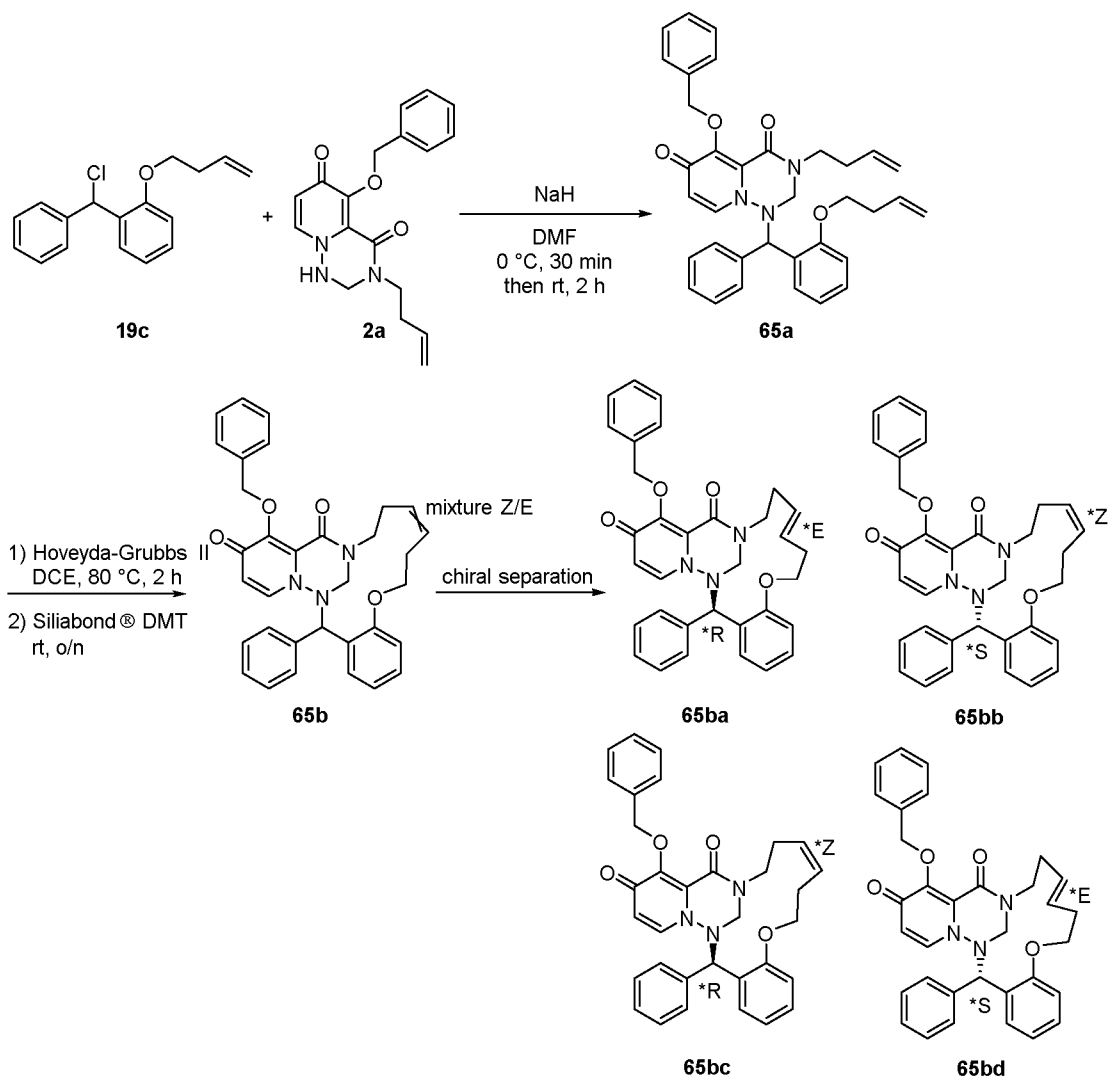
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.96 (br s, 1H), 8.09 (br d, *J*=7.6 Hz, 1H), 7.40 - 7.46 (m, 1H), 7.30 - 7.39 (m, 2H), 7.17 - 7.28 (m, 2H), 6.90 - 7.12 (m, 3H), 6.09 - 6.23 (m, 1H), 5.89 (br s, 1H), 5.56 (d, *J*=7.6 Hz, 1H), 5.34 (s, 1H), 5.11 (d, *J*=13.6 Hz, 1H), 4.69 - 4.83 (m, 2H), 4.29 (br t, *J*=7.6 Hz, 1H), 4.22 (d, *J*=14.1 Hz, 1H), 3.18 (dd, *J*=13.9, 8.3 Hz, 1H).

LC/MS (method LC-C): Rt 2.55 min, MH⁺ 434

[α]_D²⁰: -643.49° (c 0.281, DMF)

Chiral HPLC (method HPLC-B): Rt 6.65 min, chiral purity 100%

- 15 Example 65: synthesis of (2**R*, **Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (Compound **65A**), (2**S*, **Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (Compound **65B**), (2**R*, **E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (Compound **65C**) and (2**S*, **E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (Compound **65D**)
- 20



Synthesis of intermediate **65a**:

5-(benzyloxy)-3-(but-3-en-1-yl)-1-((2-(but-3-en-1-yloxy)phenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **65a**, 3.52 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate **65b**:

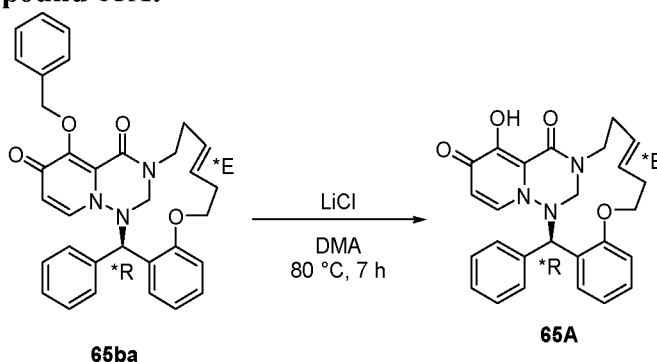
(*E/Z*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (intermediate **65b**) was obtained using the procedure described for intermediate **1f**. Crude intermediate **65b** was purified by flash chromatography over silica gel (30 μm, 80 g, CH₂Cl₂/CH₃OH from 97/3 to 95/5) to afford 1.46 g of intermediate **65b**.

The enantiomers were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5 μm 250*21.2mm, Mobile phase: 50% CO₂, 50% EtOH (10% CH₂Cl₂)) to afford a first

fraction of enantiomers **65ba** and **65bc** (546 mg) as a mixture of *E* and *Z* isomers and a second fraction of enantiomers **65bb** and **65bd** (531 mg) as a mixture of *E* and *Z* isomers. The isomers **65ba** and **65bc** were separated via chiral SFC (Stationary phase: Chiralpak AD-H 5 μ m 250*30mm, Mobile phase: 75% CO₂, 25% EtOH) to afford intermediate **65ba** (371 mg) and intermediate **65bc** (128 mg).

The isomers **65bb** and **65bd** were separated via achiral SFC (Stationary phase: AMINO 5 μ m 150*30 mm, Mobile phase: 85% CO₂, 15% (MeOH/DCM: 80/20) to afford intermediate **65bb** (326 mg) and intermediate **65bd** (148 mg).

10 Synthesis of compound **65A**:



(2**R*, **Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (compound **65A**, 101 mg) was obtained using the procedure described for compound **28A**.

15

Compound **65A**:

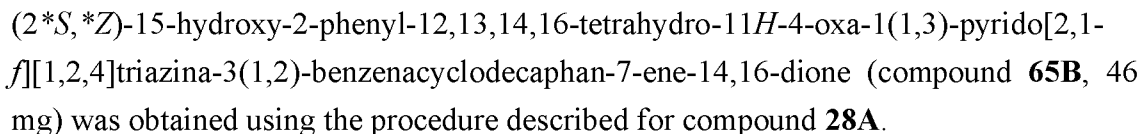
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.00 (dd, *J*=7.7, 1.1 Hz, 1H), 7.33 (td, *J*=8.8, 1.6 Hz, 1H), 7.09 - 7.19 (m, 6H), 7.06 (d, *J*=8.2 Hz, 1H), 7.00 (br s, 1H), 5.85 (s, 1H), 5.59 - 5.68 (m, 1H), 5.36 (d, *J*=7.9 Hz, 1H), 5.10 - 5.17 (m, 1H), 5.08 (d, *J*=12.9 Hz, 1H), 4.39 (br dt, *J*=11.6, 3.3 Hz, 1H), 4.26 (d, *J*=12.9 Hz, 1H), 4.06 (td, *J*=11.3, 2.7 Hz, 1H), 3.75 (br d, *J*=13.2 Hz, 1H), 2.85 - 2.93 (m, 1H), 2.75 - 2.85 (m, 1H), 2.37 - 2.45 (m, 1H), 2.20 - 2.27 (m, 1H), 2.12 - 2.20 (m, 1H).

LC/MS (method LC-C): Rt 2.78 min, MH⁺ 444

[α]_D²⁰: +339.11° (c 0.225, DMF)

25

Synthesis of compound **65B**:



10

$$[\alpha]_{\text{D}}^{20}: -324.51^{\circ} (\text{c } 0.204, \text{DMF})$$

15

(2^{*}*R*,^{*}*E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (compound **65C**, 45 mg) was obtained using the procedure described for compound **28A**.

25

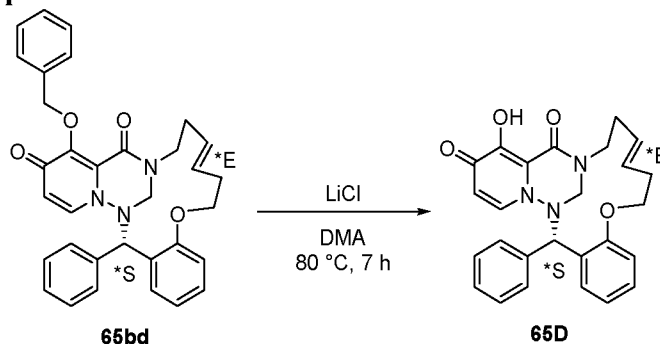
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 (d, *J*=6.9 Hz, 1H), 7.33 - 7.38 (m, 1H), 7.11 - 7.20 (m, 6H), 7.07 (d, *J*=7.6 Hz, 1H), 6.95 - 7.04 (br s, 1H), 5.72 (br t, *J*=9.9 Hz, 1H), 5.58 - 5.64 (m, 1H), 5.57 (s, 1H), 5.41 (d, *J*=7.6 Hz, 1H), 5.05 (d, *J*=13.2 Hz, 1H), 4.62

(br d, $J=12.3$ Hz, 1H), 4.35 (d, $J=13.2$ Hz, 1H), 4.21 - 4.29 (m, 1H), 3.88 (br t, $J=12.0$ Hz, 1H), 2.78 (br d, $J=14.2$ Hz, 1H), 2.40 - 2.47 (m, 1H), 1.99 - 2.06 (m, 1H), 1.83 - 1.98 (m, 2H).

LC/MS (method LC-C): Rt 2.80 min, MH⁺ 444

5 $[\alpha]_{\text{D}}^{20}$: +315.85° (c 0.183, DMF)

Synthesis of compound 65D:



(2**S*, **E*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-7-ene-14,16-dione (compound **65D**, 116 mg) was obtained using the procedure described for compound **28A**.

Compound 65D:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.00 (br d, *J*=7.6 Hz, 1H), 7.30 - 7.38 (m, 1H), 7.10 - 7.20 (m, 6H), 7.07 (br d, *J*=8.2 Hz, 1H), 6.93 - 7.05 (m, 1H), 5.86 (s, 1H), 5.60 - 5.69 (m, 1H), 5.37 (d, *J*=7.9 Hz, 1H), 5.11 - 5.18 (m, 1H), 5.09 (d, *J*=12.9 Hz, 1H), 4.37 - 4.44 (m, 1H), 4.26 (d, *J*=12.9 Hz, 1H), 4.06 (td, *J*=11.3, 2.4 Hz, 1H), 3.76 (br d, *J*=13.2 Hz, 1H), 2.86 - 2.94 (m, 1H), 2.76 - 2.85 (m, 1H), 2.35 - 2.46 (m, 1H), 2.21 - 2.28 (m, 1H), 2.17 (br d, *J*=15.1 Hz, 1H).

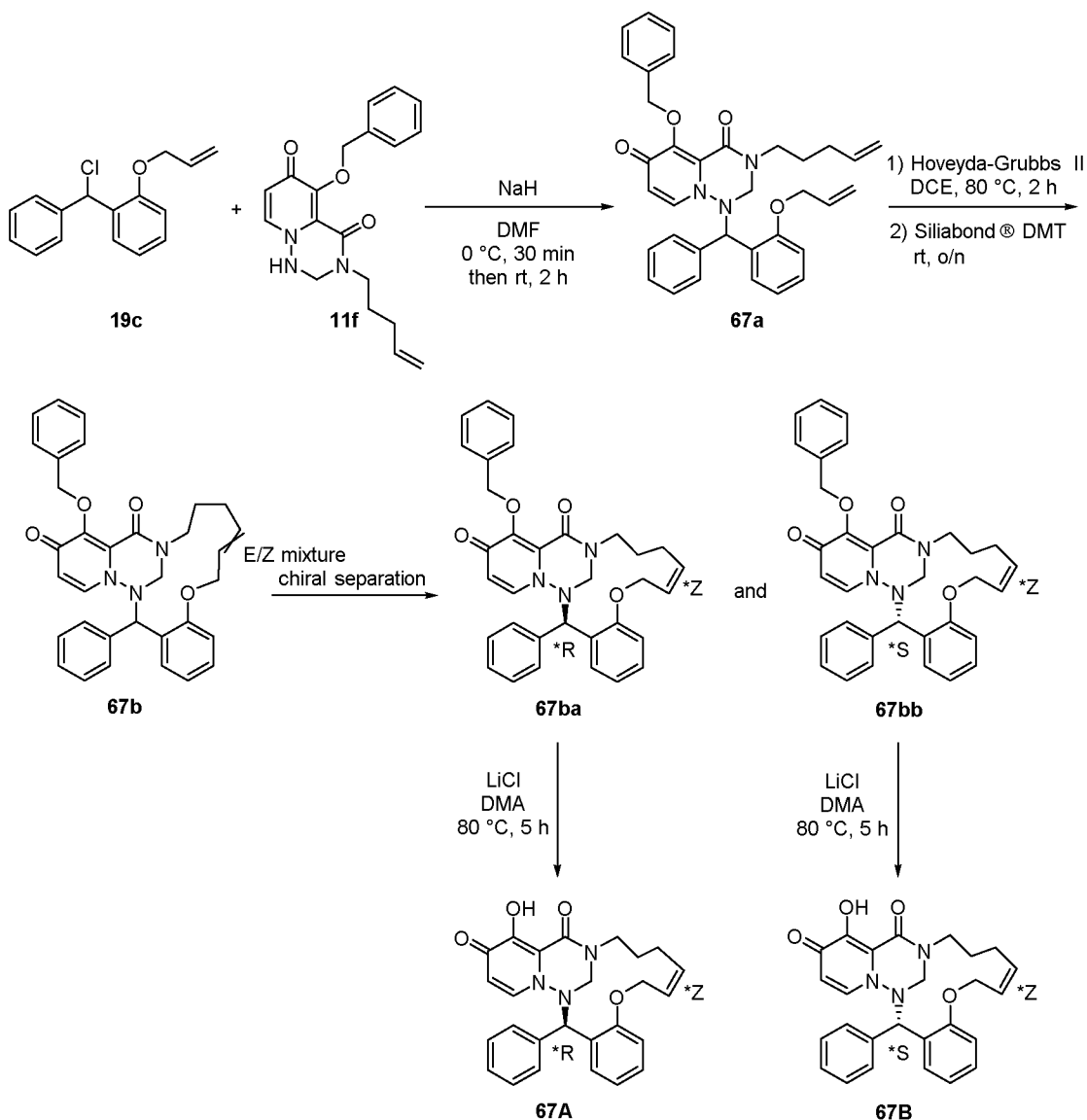
20 LC/MS (method LC-C): Rt 2.81 min, MH⁺ 444

$$[\alpha]_{\text{D}}^{20}: -345.29^{\circ} \text{ (c 0.223, DMF)}$$

Chiral HPLC (method HPLC-B): Rt 4.86 min, chiral purity 100%

Example 67: synthesis of (2**R*,**Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-6-ene-14,16-dione (Compound **67A**), (2**S*,**Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-6-ene-14,16-dione (Compound **67B**)

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**Synthesis of intermediate 67a:**

1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(pent-4-en-1-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **67a**, 3.7 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 67b:

(*E/Z*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-6-ene-14,16-dione (intermediate **67b**, mixture of *Z* and *E* isomers, 900 mg) was obtained using the procedure described for intermediate **1f**.

The isomers were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 45% CO₂, 55% MeOH) to afford the first eluted enantiomer **67ba** (335 mg) and the second eluted enantiomer **67bb** (331 mg).

Synthesis of compound 67A:

(2**R*,**Z*)-15-(benzyloxy)-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-6-ene-14,16-dione (compound **67A**, 95 mg) was obtained using the procedure described for compound **28A**.

Compound 67A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.91 (br d, *J*=6.9 Hz, 1H), 7.28 (br t, *J*=7.4 Hz, 1H), 7.16 - 7.44 (m, 5H), 7.11 (t, *J*=7.4 Hz, 1H), 7.07 (d, *J*=7.9 Hz, 1H), 6.84 (d, *J*=8.2 Hz, 1H), 5.78 (s, 1H), 5.54 - 5.68 (m, 2H), 5.48 (d, *J*=7.6 Hz, 1H), 5.01 (d, *J*=13.2 Hz, 1H), 4.92 (br d, *J*=15.4 Hz, 1H), 4.57 (br dd, *J*=15.1, 5.0 Hz, 1H), 4.45 (br d, *J*=13.2 Hz, 1H), 4.07 (br t, *J*=13.1 Hz, 1H), 2.78 - 2.88 (m, 1H), 2.73 (br d, *J*=13.9 Hz, 1H), 1.79 - 1.89 (m, 1H), 1.37 (br t, *J*=13.1 Hz, 1H), 0.55 (q, *J*=13.0 Hz, 1H).

LC/MS (method LC-A): Rt 2.85 min, MH⁺ 444

Chiral HPLC (method HPLC-B): Rt 4.89 min, chiral purity 100%

Synthesis of compound 67B:

(2**S*,**Z*)-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclodecaphan-6-ene-14,16-dione (compound **67B**, 141 mg) was obtained using the procedure described for compound **28A**.

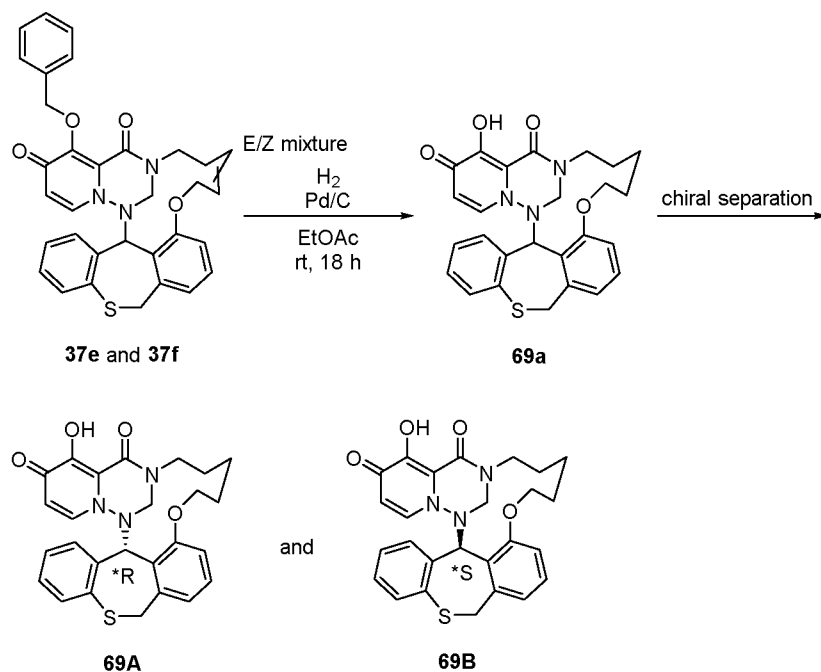
Compound 67B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.91 (dd, *J*=7.6, 1.3 Hz, 1H), 7.25 - 7.30 (m, 1H), 7.15 - 7.37 (m, 5H), 7.11 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=7.6 Hz, 1H), 6.84 (d, *J*=8.5 Hz, 1H), 5.78 (s, 1H), 5.55 - 5.67 (m, 2H), 5.48 (d, *J*=7.6 Hz, 1H), 5.01 (d, *J*=13.6 Hz, 1H), 4.92 (br dd, *J*=15.3, 1.7 Hz, 1H), 4.57 (dd, *J*=15.1, 5.4 Hz, 1H), 4.45 (d, *J*=13.6 Hz, 1H), 4.07 (br t, *J*=12.9 Hz, 1H), 2.78 - 2.88 (m, 1H), 2.73 (br d, *J*=14.2 Hz, 1H), 1.84 (br t, *J*=12.8 Hz, 1H), 1.37 (br t, *J*=13.2 Hz, 1H), 0.55 (q, *J*=13.7 Hz, 1H).

LC/MS (method LC-A): Rt 2.85 min, MH⁺ 444

Chiral HPLC (method HPLC-B): Rt 5.26 min, chiral purity 100%

Example 69: synthesis of (23b**R*)-6-hydroxy-10,11,12,13,18,23b-hexahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (Compound **69A**), (23b**S*)-6-hydroxy-10,11,12,13,18,23b-hexahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (Compound **69B**)



Synthesis of intermediate **69a**:

6-hydroxy-10,11,12,13,18,23*b*-hexahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (intermediate **69a**, 190 mg) was obtained using the procedure described for compound **2**. Purification was carried out by flash chromatography over silica gel (15 μm, 12 g, CH₂Cl₂/MeOH from 99/1 to 93/7) to afford intermediate **69a** (112 mg) as a mixture of enantiomers.

Synthesis of compounds **69A** and **69B**:

The enantiomers **69A** and **69B** were separated via Prep Chiral HPLC (Stationary phase: Daicel Chiralpak IG 20 μm 250 gram, Mobile phase: Ethanol + 0.1 % TFA) to afford the first eluted enantiomer **69A** (49 mg) and the second eluted enantiomer **69B** (49 mg).

Enantiomer **69A** was freeze-dried (water/CH₃CN, 4/1) overnight to give (23*b***R*)-6-hydroxy-10,11,12,13,18,23*b*-hexahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (compound **69A**, 33 mg).

Enantiomer **69B** was freeze-dried (water/CH₃CN, 4/1) overnight to give (23*b***S*)-6-hydroxy-10,11,12,13,18,23*b*-hexahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (compound **69B**, 34 mg).

Compound **69A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.80 (br s, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.36 (t, *J*=7.9 Hz, 1H), 7.08 - 7.13 (m, 1H), 7.00 - 7.07 (m, 3H), 6.84 (t, *J*=7.3 Hz, 1H), 6.73 (d,

$J=7.6$ Hz, 1H), 6.05 (s, 1H), 5.87 (d, $J=13.6$ Hz, 1H), 5.65 (d, $J=7.9$ Hz, 1H), 5.01 (d, $J=13.2$ Hz, 1H), 4.37 (br dd, $J=9.0$, 6.8 Hz, 1H), 4.29 (d, $J=13.2$ Hz, 1H), 4.13 (br t, $J=12.6$ Hz, 1H), 3.81 - 3.90 (m, 2H), 2.82 (br d, $J=13.6$ Hz, 1H), 2.05 - 2.15 (m, 1H), 1.82 - 1.93 (m, 1H), 1.55 - 1.70 (m, 2H), 1.35 - 1.45 (m, 1H), 1.15 - 1.29 (m, 1H).

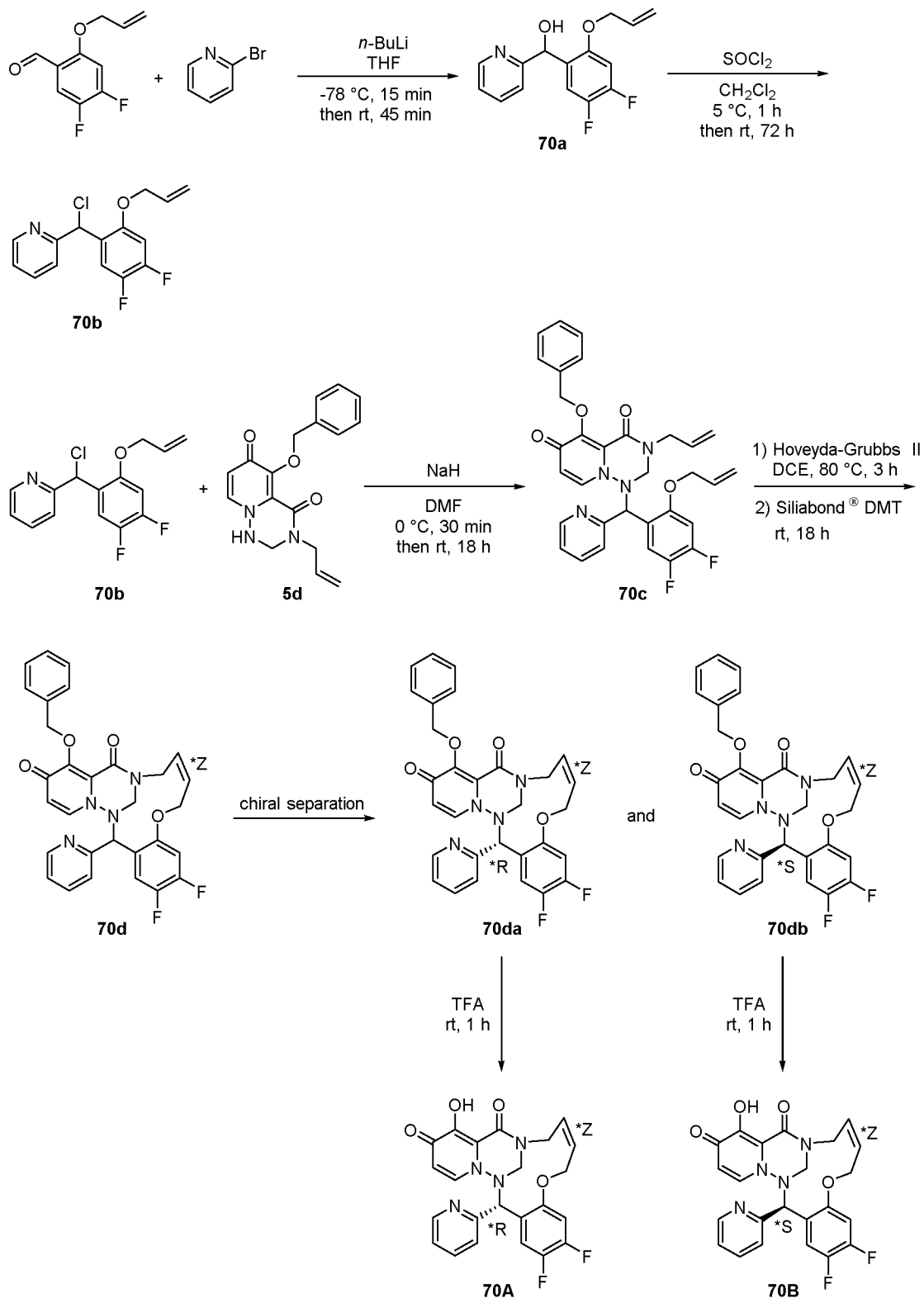
- 5 LC/MS (method LC-A): Rt 2.85 min, MH^+ 476
[α]_D²⁰: +174.8° (c 0.127, DMF)

Compound 69B:

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.84 (br s, 1H), 7.46 (d, $J=7.6$ Hz, 1H), 7.36 (t, $J=7.9$ Hz, 1H), 7.08 - 7.13 (m, 1H), 6.99 - 7.08 (m, 3H), 6.84 (t, $J=7.4$ Hz, 1H), 6.73 (d, $J=7.3$ Hz, 1H), 6.05 (s, 1H), 5.87 (d, $J=13.6$ Hz, 1H), 5.64 (d, $J=7.6$ Hz, 1H), 5.01 (d, $J=13.6$ Hz, 1H), 4.36 (br dd, $J=9.1$, 6.6 Hz, 1H), 4.29 (d, $J=13.6$ Hz, 1H), 4.13 (br t, $J=13.4$ Hz, 1H), 3.81 - 3.90 (m, 2H), 2.82 (br d, $J=13.9$ Hz, 1H), 2.05 - 2.15 (m, 1H), 1.81 - 1.93 (m, 1H), 1.55 - 1.70 (m, 2H), 1.35 - 1.45 (m, 1H), 1.20 - 1.29 (m, 1H).
- 10
15 LC/MS (method LC-A): Rt 2.84 min, MH^+ 476
[α]_D²⁰: -184° (c 0.125, DMF)

- Example 70: synthesis of (18^{*R},^{*Z})-2,3-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **70A**), (18^{*S},^{*Z})-2,3-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **70B**)
- 20

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**Synthesis of intermediate 70a:**

(2-(allyloxy)-4,5-difluorophenyl)(pyridin-2-yl)methanol (intermediate **70a**, 2.2 g) was
 5 obtained using the procedure described for intermediate **23a**. Crude intermediate **70a** was

purified by preparative LC (Stationary phase: regular SiOH, 30 μ m, Interchim[®] 120 g, Mobile phase: CH₂Cl₂/MeOH from 100/0 to 99/1).

Synthesis of intermediate 70b:

- 5 2-((2-(allyloxy)-4,5-difluorophenyl)chloromethyl)pyridine (intermediate **70b**, 2.3 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 70c:

- 10 3-allyl-1-((2-(allyloxy)-4,5-difluorophenyl)(pyridin-2-yl)methyl)-5-(benzyloxy)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **70c**, 1.5g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 70d:

- 15 (*Z)-12-(benzyloxy)-2,3-difluoro-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **70d**, 0.68 g) was obtained using the procedure described for intermediate **1f**. A second purification was performed via reverse phase (Stationary phase: YMC-actus Triart C18 10 μ m 30*150mm, Mobile phase: 0.2% aq.NH₄CO₃/CH₃CN from 65/35 to 25/75) to afford 0.36 g of intermediate **70d**.
- 20 The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK IC 5 μ m 250*30mm, Mobile phase: 40% CO₂, 60% (MeOH+20%DCM) to afford the first eluted enantiomer **70da** (163 mg) and the second eluted enantiomer **70db** (163 mg).

25 **Synthesis of compound 70A:**

(18^{*}*R*, *Z)-2,3-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **70A**, 91 mg) was obtained using the procedure described for compound **1**.

30 **Compound 70A:**

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.41 (br d, *J*=4.1 Hz, 1H), 8.14 (br t, *J*=10.7 Hz, 1H), 7.65 (td, *J*=7.6, 1.3 Hz, 1H), 7.48 (br dd, *J*=11.7, 7.3 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 7.24 (dd, *J*=6.9, 5.0 Hz, 1H), 7.19 (br d, *J*=7.6 Hz, 1H), 6.11 - 6.21 (m, 1H), 6.05 (br s, 1H), 5.55 (d, *J*=7.6 Hz, 1H), 5.45 (s, 1H), 5.11 (d, *J*=13.9 Hz, 1H), 4.79 (br dd, *J*=13.6, 4.4 Hz, 1H), 4.73 (dd, *J*=10.7, 7.3 Hz, 1H), 4.36 - 4.44 (m, 1H), 4.32 (d, *J*=13.9 Hz, 1H), 3.18 (br dd, *J*=13.6, 8.5 Hz, 1H).

LC/MS (method LC-A): Rt 2.37 min, MH⁺ 453

[α]_D²⁰: +628.83° (c 0.111, DMF)

Chiral HPLC (method HPLC-B): Rt 4.38 min, chiral purity 100%

Synthesis of compound 70B:

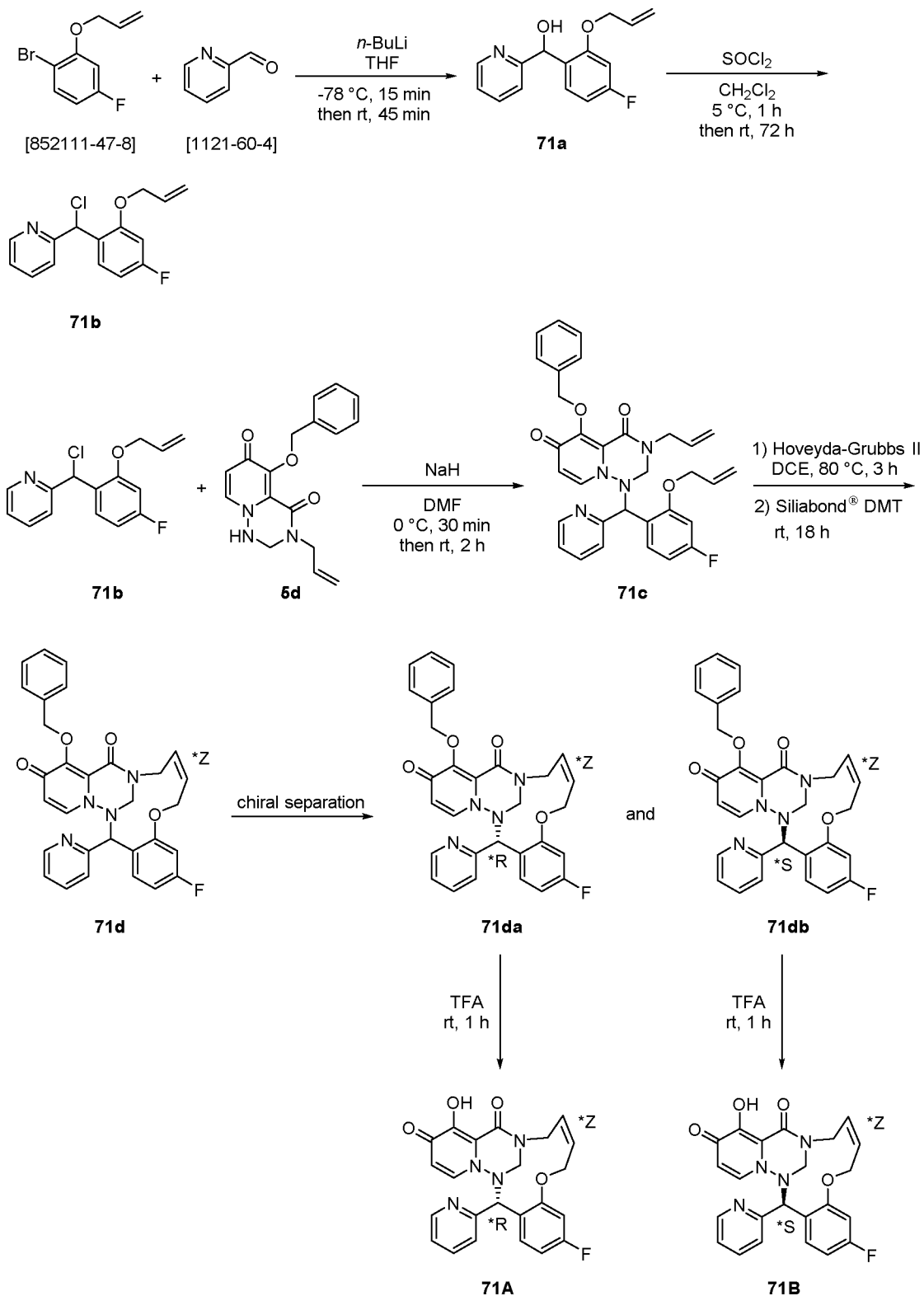
- 5 (18*S,*Z)-2,3-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound 70B, 94 mg) was obtained using the procedure described for compound 1.

Compound 70B:

- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.41 (br d, *J*=3.8 Hz, 1H), 8.14 (br t, *J*=10.6 Hz, 1H), 7.65 (td, *J*=7.6, 1.3 Hz, 1H), 7.48 (br dd, *J*=11.8, 7.4 Hz, 1H), 7.27 (br d, *J*=7.6 Hz, 1H), 7.24 (dd, *J*=7.1 Hz, 1H), 7.17 (br d, *J*=7.6 Hz, 1H), 6.11 - 6.21 (m, 1H), 6.05 (br s, 1H), 5.51 (d, *J*=7.6 Hz, 1H), 5.45 (br s, 1H), 5.11 (d, *J*=13.9 Hz, 1H), 4.79 (br dd, *J*=13.7, 4.3 Hz, 1H), 4.73 (br dd, *J*=10.1, 7.6 Hz, 1H), 4.36 - 4.44 (m, 1H), 4.32 (d, *J*=13.9 Hz, 1H), 3.18 (br dd, *J*=13.6, 8.5 Hz, 1H).
- 15 LC/MS (method LC-A): Rt 2.36 min, MH⁺ 453
[α]_D²⁰: -609.82° (c 0.163, DMF)
Chiral HPLC (method HPLC-B): Rt 4.71 min, chiral purity 100%

- 20 Example 71: synthesis of (18*R,*Z)-3-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound 71A), (18*S,*Z)-3-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound 71B)

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**Synthesis of intermediate 71a:**

(2-(allyloxy)-4-fluorophenyl)(pyridin-2-yl)methanol (intermediate **71a**, 0.26 g) was
 5 obtained using the procedure described for intermediate **23a**. Crude intermediate **71a** was

purified by preparative LC (Stationary phase: regular SiOH, 30 μ m, 80 g Interchim[®], Mobile phase: CH₂Cl₂).

Synthesis of intermediate 71b:

- 5 2-((2-(allyloxy)-4-fluorophenyl)chloromethyl)pyridine (intermediate **71b**, 280 mg) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 71c:

- 10 3-allyl-1-((2-(allyloxy)-4-fluorophenyl)(pyridin-2-yl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **71c**, 0.43 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 71d:

- 15 (**Z*)-12-(benzyloxy)-3-fluoro-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **71d**, 0.17 g) was obtained using the procedure described for intermediate **1f**. Purification was carried out by flash chromatography over silica gel (30 μ m, 24 g, CH₂Cl₂/MeOH from 100/0 to 98/2). A second purification via Reverse phase (Stationary phase: YMC-actus Triart C18 10 μ m 30*150mm, Mobile phase: 0.2% aq.NH₄HCO₃/CH₃CN from 75/25 to 35/65) was performed yielding 80 mg of **71d**.
20 The enantiomers were separated by chiral SFC (Stationary phase: Chiralcel OD-H 5 μ m 250x21.2mm, Mobile phase: 60% CO₂, 40% EtOH) to give the first eluted enantiomer **71da** (40 mg) and the second eluted enantiomer **71db** (39 mg).

25 **Synthesis of compound 71A:**

(18**R*,**Z*)-3-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **71A**, 18 mg) was obtained using the procedure described for compound **1**.

30 **Compound 71A:**

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.32 (br d, *J*=4.1 Hz, 1H), 8.06 - 8.14 (m, 1H), 7.56 (td, *J*=7.7, 1.6 Hz, 1H), 7.09 - 7.19 (m, 4H), 7.04 (d, *J*=7.9 Hz, 1H), 6.03 - 6.12 (m, 1H), 5.92 (br s, 1H), 5.42 (d, *J*=7.9 Hz, 1H), 5.39 (s, 1H), 5.02 (d, *J*=13.9 Hz, 1H), 4.64 - 4.74 (m, 2H), 4.35 (br dd, *J*=10.1, 8.2 Hz, 1H), 4.16 (d, *J*=13.9 Hz, 1H), 3.09 - 3.15 (m, 35 1H).

LC/MS (method LC-C): Rt 2.24 min, MH⁺ 435

[α]_D²⁰: -666.96° (c 0.115, DMF)

Chiral HPLC (method HPLC-B): Rt 5.50 min, chiral purity 100%

Synthesis of compound 71B:

(18^{*}*R*,^{*}*Z*)-3-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

5 (compound **71B**, 20 mg) was obtained using the procedure described for compound **1**.

Compound 71B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.32 (br d, *J*=3.8 Hz, 1H), 8.10 (br t, *J*=8.0 Hz, 1H), 7.56 (br t, *J*=7.4 Hz, 1H), 7.09 - 7.20 (m, 4H), 7.04 (d, *J*=7.6 Hz, 1H), 6.03 - 6.12
10 (m, 1H), 5.93 (br s, 1H), 5.42 (d, *J*=7.6 Hz, 1H), 5.39 (s, 1H), 5.02 (br d, *J*=13.6 Hz, 1H), 4.63 - 4.75 (m, 2H), 4.35 (br dd, *J*=9.9, 8.0 Hz, 1H), 4.16 (br d, *J*=13.9 Hz, 1H), 3.09 - 3.16 (m, 1H).

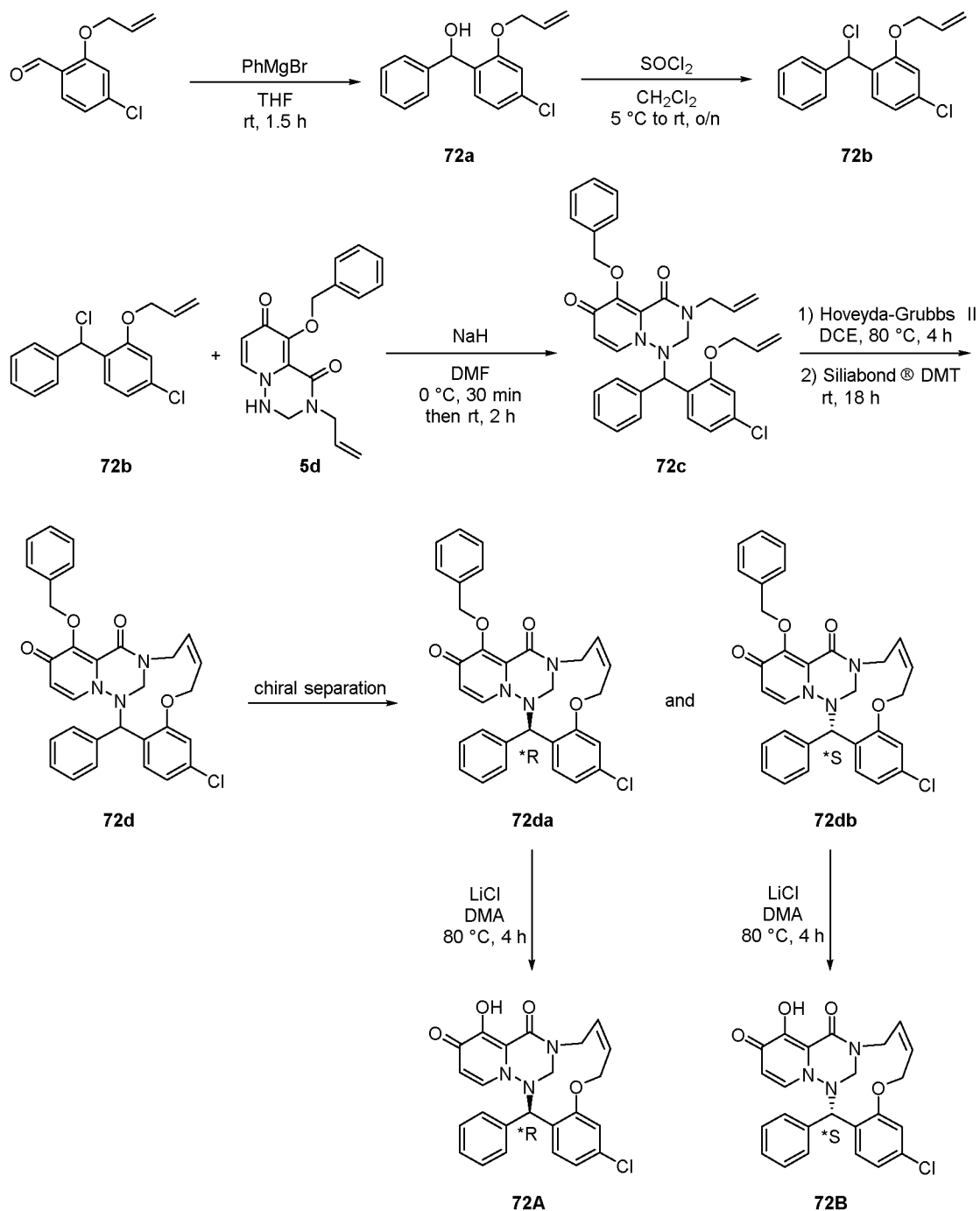
LC/MS (method LC-C): Rt 2.24 min, MH⁺ 435

[α]_D²⁰: +647.77 ° (c 0.156, DMF)

15 Chiral HPLC (method HPLC-B): Rt 5.07 min, chiral purity 100%

Example 72: synthesis of (18^{*}*R*,*Z*)-3-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **72A**), (18^{*}*S*,*Z*)-3-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-
20 methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **72B**)

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**Synthesis of intermediate 72a:**

(2-(allyloxy)-4-chlorophenyl)(phenyl)methanol (**intermediate 72a**, 5.00 g) was obtained using the procedure described for intermediate **2b**. Crude intermediate **72a** was purified by flash column chromatography on silica gel (15-40 μm , 120 g, heptane/EtOAc from 90/10 to 80/20).

Synthesis of intermediate 72b:

2-(allyloxy)-4-chloro-1-(chloro(phenyl)methyl)benzene (**intermediate 72b**, 2.3 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 72c:

3-allyl-1-((2-(allyloxy)-4-chlorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **72c**, 2.5 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 72d:

(Z)-12-(benzyloxy)-3-chloro-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **72d**, 1.8 g) was obtained using the procedure described for intermediate **1f**. Crude intermediate **72d** was purified by flash chromatography over silica gel (20-45 μ m, 20 g, CH₂Cl₂/CH₃OH from 99/1 to 97/3) to afford intermediate **72d** (380 mg). The enantiomers were separated via chiral SFC (Stationary phase: CHIRACEL OJ-H 5 μ m 250*30mm, Mobile phase: 70% CO₂, 30% CH₃OH) to give the first eluted enantiomer **72da** (140 mg) and the second eluted enantiomer **72db** (135 mg).

Synthesis of compound 72A

(18**R,Z*)-3-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **72A**, 54 mg) was obtained using the procedure described for compound **28A**.

Compound 72A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.13 (d, *J*=8.2 Hz, 1H), 7.41 - 7.45 (m, 1H), 7.39 - 7.41 (m, 1H), 7.25 (br d, *J*=7.9 Hz, 1H), 7.06 - 7.22 (m, 5H), 6.11 - 6.20 (m, 1H), 5.99 (br s, 1H), 5.49 (d, *J*=7.6 Hz, 1H), 5.28 (s, 1H), 5.10 (d, *J*=13.9 Hz, 1H), 4.72 - 4.82 (m, 2H), 4.35 - 4.44 (m, 1H), 4.25 (d, *J*=13.9 Hz, 1H), 3.20 (br dd, *J*=13.9, 8.5 Hz, 1H).

LC/MS (method LC-C): Rt 2.79 min, MH⁺ 450

$[\alpha]_D^{20}$: +685.35 ° (c 0.198, DMF)

Chiral HPLC (method HPLC-B): Rt 5.39 min, chiral purity 100%

Synthesis of compound 72B:

(18**S,Z*)-3-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **72B**, 56 mg) was obtained using the procedure described for compound **28A**.

Compound 72B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.12 (d, *J*=8.2 Hz, 1H), 7.42 (dd, *J*=8.5, 1.9 Hz, 1H), 7.39 - 7.41 (m, 1H), 7.24 (br d, *J*=7.6 Hz, 1H), 7.09 - 7.22 (m, 5H), 6.10 - 6.20 (m,

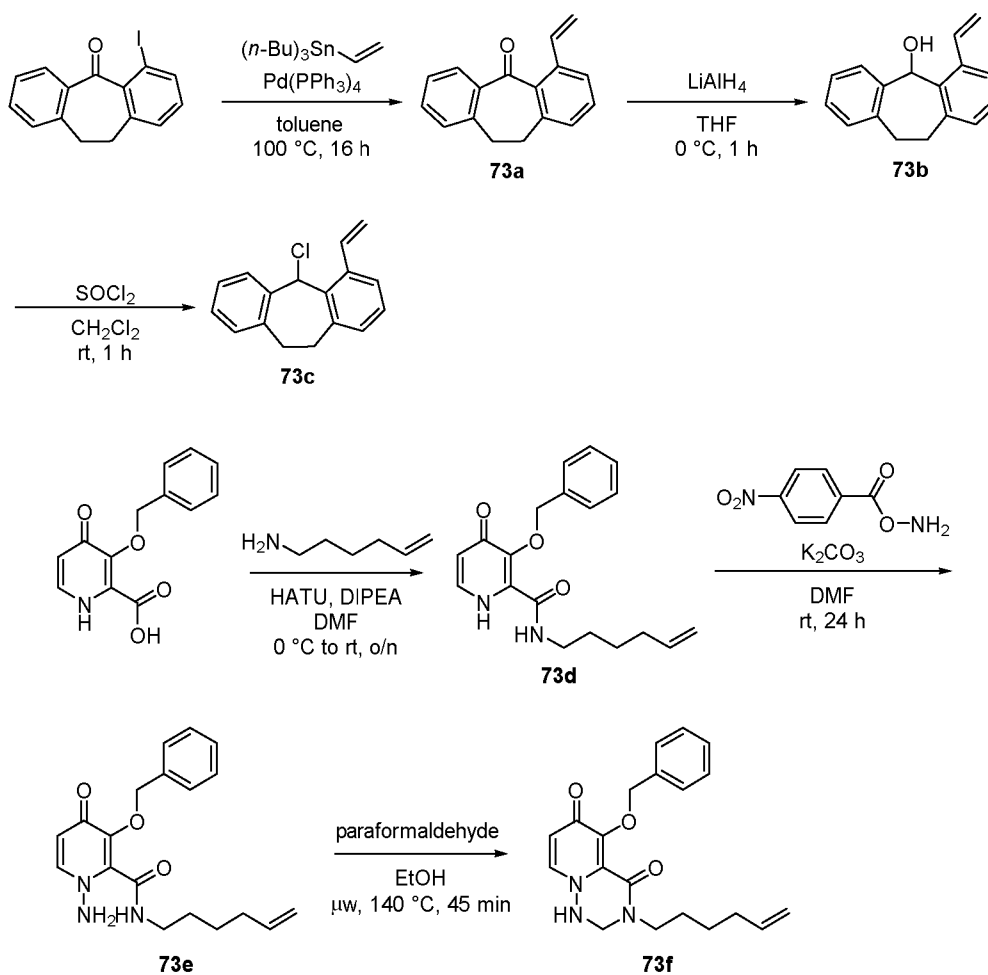
1H), 5.98 (br s, 1H), 5.48 (d, $J=7.6$ Hz, 1H), 5.27 (s, 1H), 5.10 (d, $J=13.6$ Hz, 1H), 4.71 - 4.83 (m, 2H), 4.36 - 4.44 (m, 1H), 4.24 (d, $J=13.9$ Hz, 1H), 3.19 (br dd, $J=13.9, 8.5$ Hz, 1H).

LC/MS (method LC-C): Rt 2.79 min, MH^+ 450

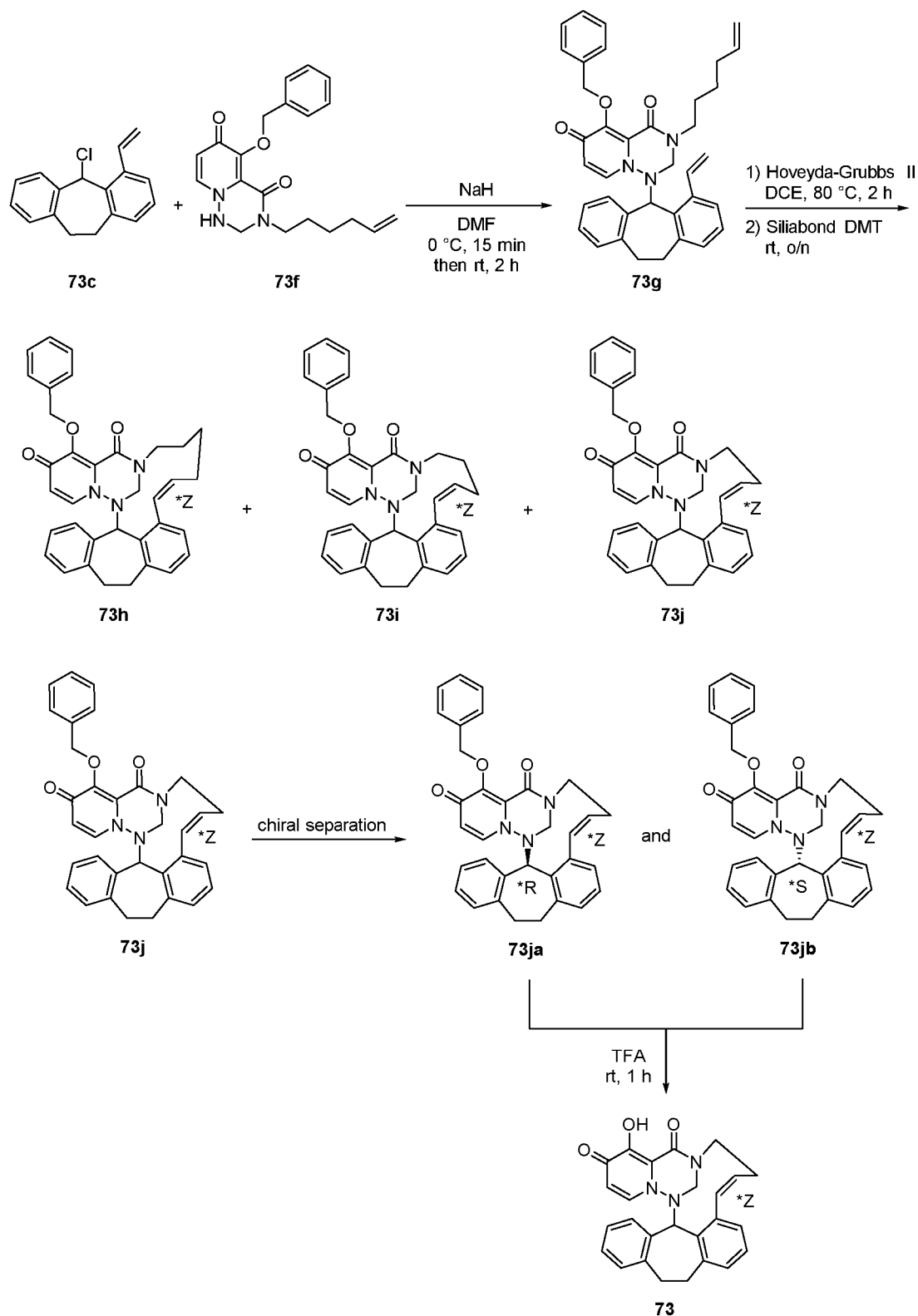
5 $[\alpha]_D^{20}$: -692.86 ° (c 0.210, DMF)

Chiral HPLC (method HPLC-B): Rt 7.11 min, chiral purity 100%

10 Example 73: synthesis of (11 $\ast$ *Z*)-6-hydroxy-10,16,17,21*b*-tetrahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*op*]pyrido[1,2-*c*][2,3,6]benzotriazacyclododecine-5,7-dione (Compound **73**)



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Synthesis of intermediate 73a:

- 5 To a stirred solution of 4-iodo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-one [CAS 70911-04-5] (3.40 g, 10.2 mmol) and Pd(PPh₃)₄ (1.18 g, 1.02 mmol) in toluene (146 mL) was added tributyl(vinyl)tin (8.9 mL, 30.5 mmol). The reaction mixture was stirred at 100 °C for 16 h. The mixture was concentrated in vacuo. The residue was extracted with

CH₂Cl₂, washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash column chromatography over silica gel (petroleum ether/EtOAc from 100/0 to 90/10) to afford 4-vinyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (intermediate **73a**, 2.15 g).

5

Synthesis of intermediate 73b:

Intermediate **73a** (1.50 g, 6.40 mmol) was dissolved in anhydrous THF (30mL) under nitrogen atmosphere. The solution was cooled to 0 °C and LiAlH₄ (1.0 M in THF, 6.4 mL, 6.40 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by the careful addition of water (250 µL), then a 15% aqueous solution of NaOH and water (750 µL) were added. The precipitate was filtered over Celite[®]. The filter-cake was washed with EtOAc. The filtrate was dried over Na₂SO₄, filtered and concentrated in vacuo to afford 4-vinyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (intermediate **73b**, 1.51 g).

15

Synthesis of intermediate 73c:

5-chloro-4-vinyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene (intermediate **73c**, 1.63 g) was obtained using the procedure described for intermediate **5a**.

20 **Synthesis of intermediate 73d:**

3-(benzyloxy)-*N*-(hex-5-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **73d**, 5.7 g) was obtained using the procedure described for intermediate **5b**.

25 **Synthesis of intermediate 73e:**

To a solution of intermediate **73d** (5.70 g, 17.5 mmol) in anhydrous DMF (200 mL) was suspended K₂CO₃ (7.24 g, 52.4 mmol) at rt. The mixture was stirred for 5 min. O-(4-Nitrobenzoyl)hydroxylamine (4.77 g, 26.2 mmol) was added and the reaction mixture was stirred at rt for 24 h. The reaction mixture was diluted with water. The mixture was extracted with CH₂Cl₂ (3 times), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was taken up in EtOAc. The precipitate was filtered off and dried under vacuum to afford 1-amino-3-(benzyloxy)-*N*-(hex-5-en-1-yl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **73e**, 4.6 g).

35 **Synthesis of intermediate 73f:**

Paraformaldehyde (223 mg, 7.41 mmol) was added to a solution of intermediate **73e** (2.30 g, 3.34 mmol) in EtOH (15 mL). The reaction mixture was stirred at 140 °C for 45 min in a microwave oven. The mixture was concentrated in vacuo. The crude mixture

was purified by flash chromatography over silica gel (220 g, CH₂Cl₂/MeOH from 100/0 to 90/10) to afford 5-(benzyloxy)-3-(hex-5-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **73f**, 1.9 g).

5 **Synthesis of intermediate 73g:**

5-(benzyloxy)-3-(hex-5-en-1-yl)-1-(4-vinyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **73g**, 170 mg) was obtained using the procedure described for intermediate **2d**.

10 **Synthesis of intermediates 73h, 73i and 73j**

A mixture of (13**Z*)-6-(benzyloxy)-10,11,12,18,19,23*b*-hexahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-*c*][2,3,6]benzotriazacyclotetradecine-5,7-dione (intermediate **73h**), (12**Z*)-6-(benzyloxy)-9,10,11,17,18,22*b*-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-

15 *pq*]pyrido[1,2-*c*][2,3,6]benzotriazacyclotridecine-5,7-dione (intermediate **73i**) and (11**Z*)-6-(benzyloxy)-10,16,17,21*b*-tetrahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*op*]pyrido[1,2-*c*][2,3,6]benzotriazacyclododecine-5,7-dione (intermediate **73j**) was obtained using the procedure described for intermediate **59d**.

20 The mixture of intermediates **73h**, **73i** and **73j** (300 mg) was purified via reverse phase (Stationary phase: YMC-actus Triart C18 10µm 30*150mm, Mobile phase Gradient: from 45% 0.2% aq. NH₄HCO₃/MeCN from 45/55 to 25/75) to afford intermediate **73j** (65 mg), intermediate **73i** (118 mg) and intermediate **73h** (25 mg).

The enantiomers of **73j** were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 50% CO₂, 50% MeOH) to afford the first eluted enantiomer **73ja** (30 mg) and the second eluted enantiomer **73jb** (35 mg).

Synthesis of compound 73:

((11**Z*)-6-hydroxy-10,16,17,21*b*-tetrahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*op*]pyrido[1,2-*c*][2,3,6]benzotriazacyclododecine-5,7-dione (compound **73**, 6 mg) was obtained using the procedure described for compound **1**. Racemization occurred during the reaction and was also observed when starting from intermediate **73jb**.

35 **Compound 73:**

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.21 - 7.29 (m, 2H), 7.06 - 7.16 (m, 2H), 6.89 (br dd, *J*=7.1, 0.8 Hz, 1H), 6.85 (br d, *J*=7.6 Hz, 1H), 6.80 (br t, *J*=7.1 Hz, 1H), 6.64 (d, *J*=10.7 Hz, 1H), 6.40 (d, *J*=7.6 Hz, 1H), 5.86 (td, *J*=11.1, 4.6 Hz, 1H), 5.52 (s, 1H), 5.40

(br d, $J=7.3$ Hz, 1H), 4.76 (br d, $J=13.6$ Hz, 1H), 4.24 - 4.40 (m, 2H), 4.16 (br d, $J=13.6$ Hz, 1H), 3.46 - 3.54 (m, 1H), 2.85 - 2.94 (m, 1H), 2.67 - 2.76 (m, 2H), 2.14 - 2.25 (m, 1H), 2.03 (br d, $J=14.8$ Hz, 1H).

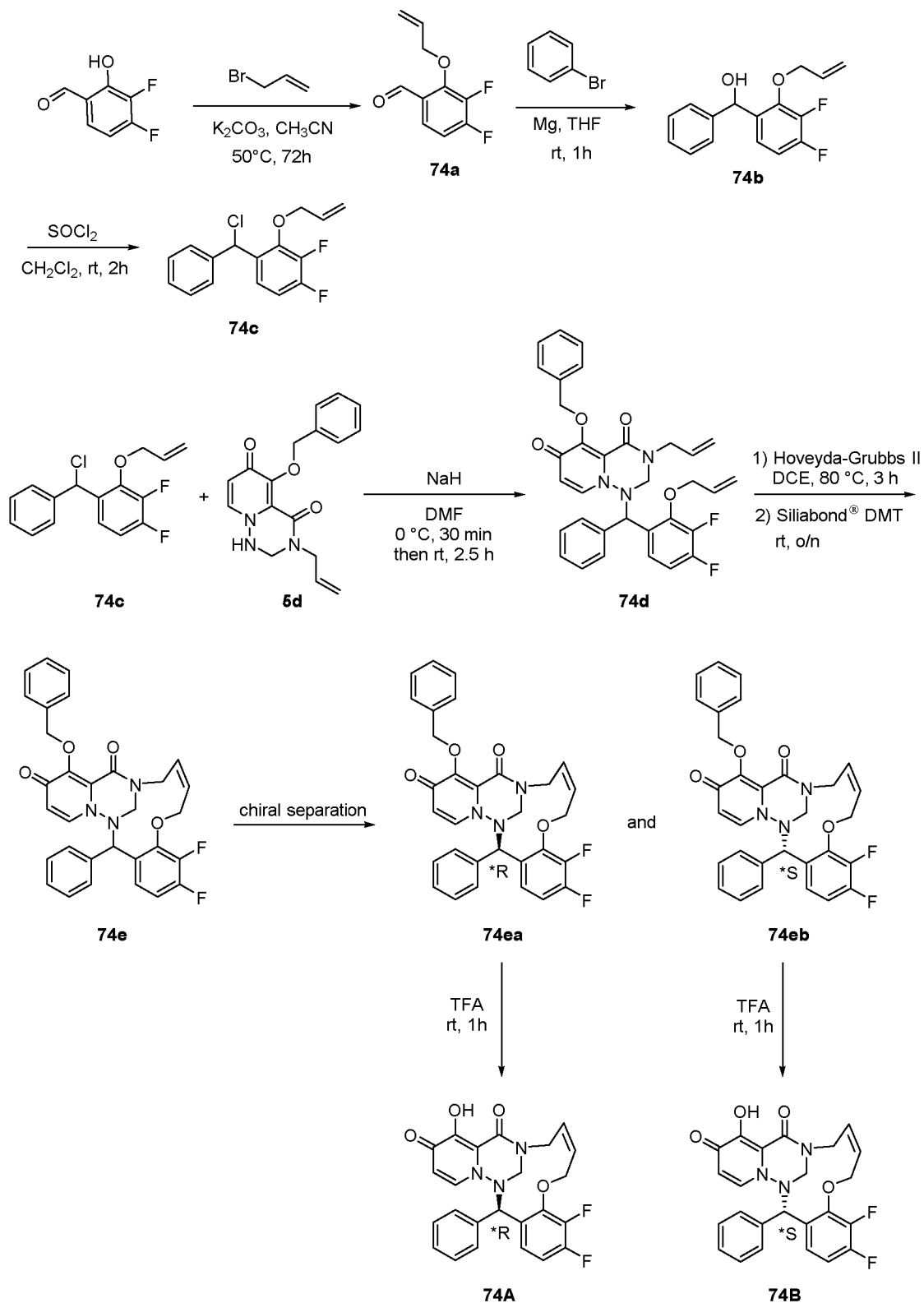
LC/MS (method LC-C): Rt 2.92 min, MH^+ 426

5

Example 74: synthesis of (18 $\ast$ *R,Z*)-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **74A**), (18 $\ast$ *S,Z*)-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

10 (Compound **74B**)

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Synthesis of intermediate 74a:

A mixture of allyl bromide (16.4 mL, 189.748 mmol), 3,4-difluoro-2-hydroxybenzaldehyde [CAS 502762-95-0] (20 g, 126.5 mmol), K₂CO₃ (34.97 g, 253 mmol) in CH₃CN (330 mL) was stirred at 50°C for 72 h. The reaction was filtered and

the filtrate was concentrated under reduced pressure. The residue was taken up with EtOAc and filtered. The filtrate was washed with water, dried over MgSO₄, filtered and the solvent was evaporated to give 2-(allyloxy)-3,4-difluorobenzaldehyde (intermediate **74a**, 24.6 g).

5

Synthesis of intermediate 74b:

Under a N₂ flow, bromobenzene (7.56 mL, 72.161 mmol) in THF (50 mL) was added dropwise to a suspension of Mg (1.76 g) in THF (25 mL). The temperature was kept under 40°C with an ice-bath and the mixture was stirred under N₂ until Mg
10 disappearance. Under N₂ flow, this solution was added dropwise at 0°C to a solution of 2-(allyloxy)-3,4-difluorobenzaldehyde (intermediate **74a**, 11 g, 55.508 mmol) in THF (50 mL). The resulting mixture was stirred at rt for 1h. The reaction was cooled down to 0°C, was quenched with NH₄Cl 10% in water and extracted with EtOAc. The organic layer was washed with water, dried over MgSO₄, filtered and the solvent was
15 concentrated under reduced pressure. Purification was carried out by flash chromatography over silica gel (220 g 30 µm, eluent Heptane/EtOAc 95/5 to 80/20). The pure fractions were collected and evaporated to dryness to give (2-(allyloxy)-3,4-difluorophenyl)(phenyl)methanol (intermediate **74b**, 11 g).

Synthesis of intermediate 74c:

SOCl₂ (2.98 mL, 40.979 mmol) was added dropwise to a solution of (2-(allyloxy)-3,4-difluorophenyl)(phenyl)methanol (intermediate **74b**, 9.44 g, 34.149 mmol) in CH₂Cl₂ (84 mL) at 5°C. The mixture was stirred at 5°C for 45 mn and at rt for 2h. The solvent was evaporated to dryness and coevaporated with toluene to give 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene (intermediate **74c**, 10.7 g), used as such in
25 the next step.

Synthesis of intermediate 74d:

3-allyl-1-((2-(allyloxy)-3,4-difluorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **74d**, 1.7 g) was
30 obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 74e:

(*Z*)-12-(benzyloxy)-3,4-difluoro-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
35 (intermediate **74e**, 1.3 g) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: CHIRACEL OJ-H 5 μ m 250*30mm, Mobile phase: 80% CO₂, 20% MeOH) to afford the first eluted enantiomer **74ea** (561 mg) and the second eluted enantiomer **74eb** (564 mg).

5 **Synthesis of compound 74A:**

(18*R,Z)-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **74A**) was obtained using the procedure described for compound **1**. Crude compound **74A** was purified by preparative LC (regular SiOH 30 μ m, 24 g, CH₂Cl₂/MeOH from 99/1 to 95/5). The residue (370 mg) was triturated in Et₂O. The solid was filtered off and dried under vacuum to give compound **74A** (311 mg).

Compound 74A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.94 (br t, *J*=6.3 Hz, 1H), 7.50 (q, *J*=8.5 Hz, 1H), 7.01 - 7.29 (m, 6H), 6.25 (br s, 1H), 6.04 (br s, 1H), 5.49 (d, *J*=7.9 Hz, 1H), 5.22 (br s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.78 - 4.91 (m, 2H), 4.27 (br d, *J*=13.9 Hz, 2H), 3.20 (br dd, *J*=13.9, 7.9 Hz, 1H).

LC/MS (method LC-C): Rt 2.68 min, MH⁺ 452

$[\alpha]_D^{20}$: +607.43 ° (c 0.202, DMF)

Chiral HPLC (method HPLC-B): Rt 5.38 min, chiral purity 100%

Synthesis of compound 74B:

(18*S,Z)-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **74B**) was obtained using the procedure described for compound **1**. Crude compound **74B** was purified by preparative LC (regular SiOH 30 μ m, 24 g, CH₂Cl₂/MeOH from 99/1 to 95/5). The residue (375 mg) was triturated in Et₂O. The solid was filtered off and dried under vacuum to give compound **74B** (320 mg).

Compound 74B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.94 (br t, *J*=6.1 Hz, 1H), 7.50 (q, *J*=8.5 Hz, 1H), 7.00 - 7.29 (m, 6H), 6.25 (br s, 1H), 6.04 (br s, 1H), 5.49 (d, *J*=7.6 Hz, 1H), 5.22 (br s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.79 - 4.90 (m, 2H), 4.27 (d, *J*=13.9 Hz, 2H), 3.20 (br dd, *J*=13.9, 8.2 Hz, 1H).

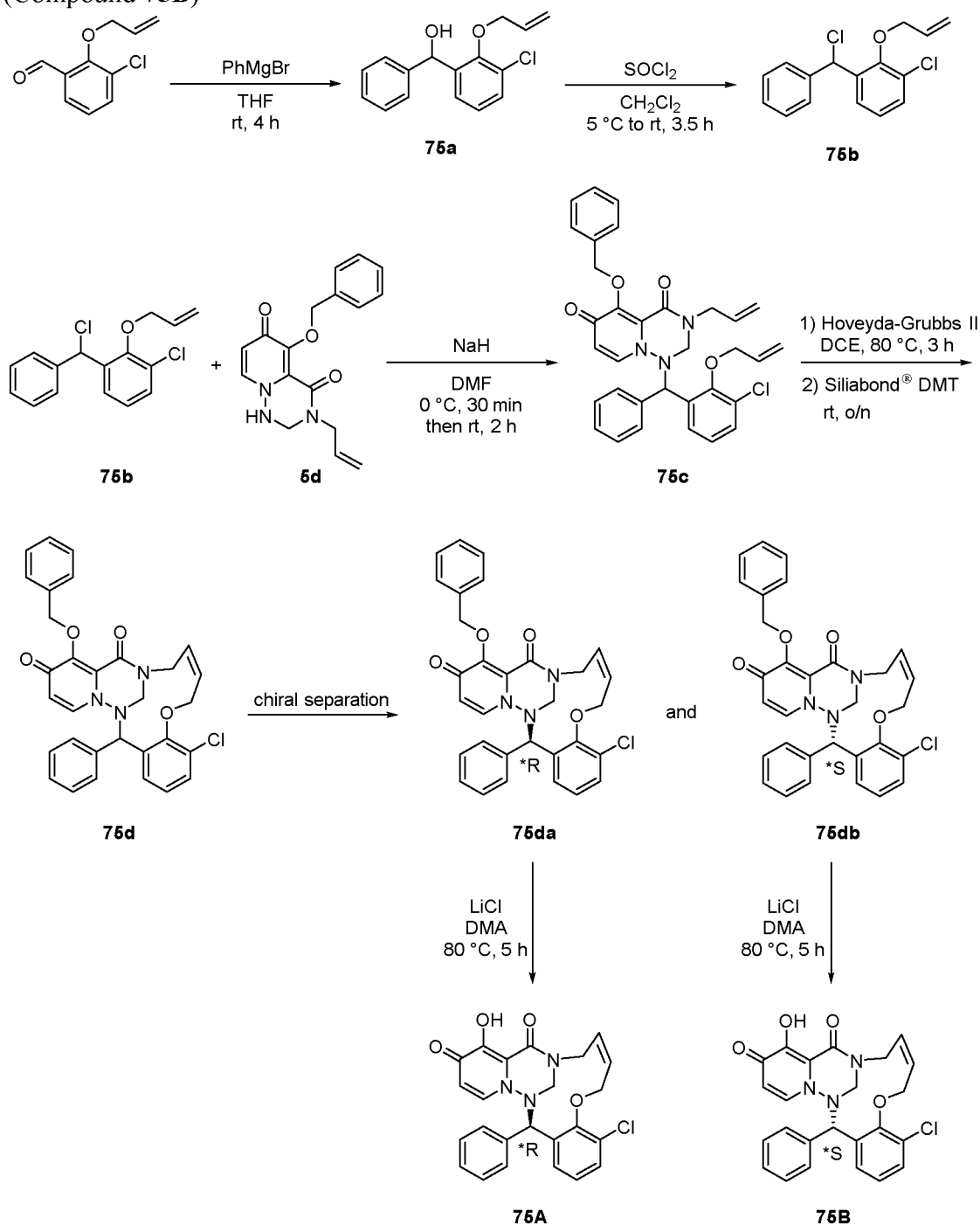
LC/MS (method LC-C): Rt 2.68 min, MH⁺ 452

$[\alpha]_D^{20}$: -634.65 ° (c 0.127, DMF)

Chiral HPLC (method HPLC-B): Rt 8.39 min, chiral purity 100%

Example 75: synthesis of (18^{*}*R,Z*)-4-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **75A**), (18^{*}*S,Z*)-4-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

5 (Compound **75B**)



Synthesis of intermediate **75a**:

(2-(allyloxy)-3-chlorophenyl)(phenyl)methanol (intermediate **75a**, 4.7 g) was obtained using the procedure described for intermediate **2b**. Crude intermediate **75a** was purified

by flash chromatography over silica gel (15-40 μ m, 220 g, heptane/EtOAc from 90/10 to 80/20).

Synthesis of intermediate 75b:

- 5 2-(allyloxy)-1-chloro-3-(chloro(phenyl)methyl)benzene (intermediate **75b**, 2.00 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 75c:

- 10 3-allyl-1-((2-(allyloxy)-3-chlorophenyl)(phenyl)methyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **75c**, 3.7 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 75d:

- 15 (Z)-12-(benzyloxy)-4-chloro-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **75d**, 2.23 g) was obtained using the procedure described for intermediate **1f**.

- 20 The enantiomers were separated via chiral SFC (Stationary phase: Chiralpak IC 5 μ m 250*21.2mm, Mobile phase: 40% CO₂, 60% (MeOH/CH₂Cl₂, 80/20) to afford the first elute enantiomer **75da** (1.01 g) and the second eluted enantiomer **75db** (916 mg).

Synthesis of compound 75A:

- 25 (18**R,Z*)-4-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **75A**, 187 mg) was obtained using the procedure described for compound **28A**.

Compound 75A:

- 30 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.01 (br d, *J*=7.6 Hz, 1H), 7.50 (dd, *J*=8.0, 1.4 Hz, 1H), 7.35 (t, *J*=8.0 Hz, 1H), 6.95 - 7.22 (m, 6H), 6.19 (br s, 1H), 5.82 (br s, 1H), 5.41 (d, *J*=7.9 Hz, 1H), 5.23 (br s, 1H), 5.09 (d, *J*=13.6 Hz, 1H), 4.69 - 4.81 (m, 2H), 4.24 (br d, *J*=13.9 Hz, 2H), 3.14 (br dd, *J*=14.0, 7.7 Hz, 1H).

LC/MS (method LC-C): Rt 2.74 min, MH⁺ 450

[α]_D²⁰: +606.45 ° (c 0.248, DMF)

- 35 **Synthesis of compound 75B:**

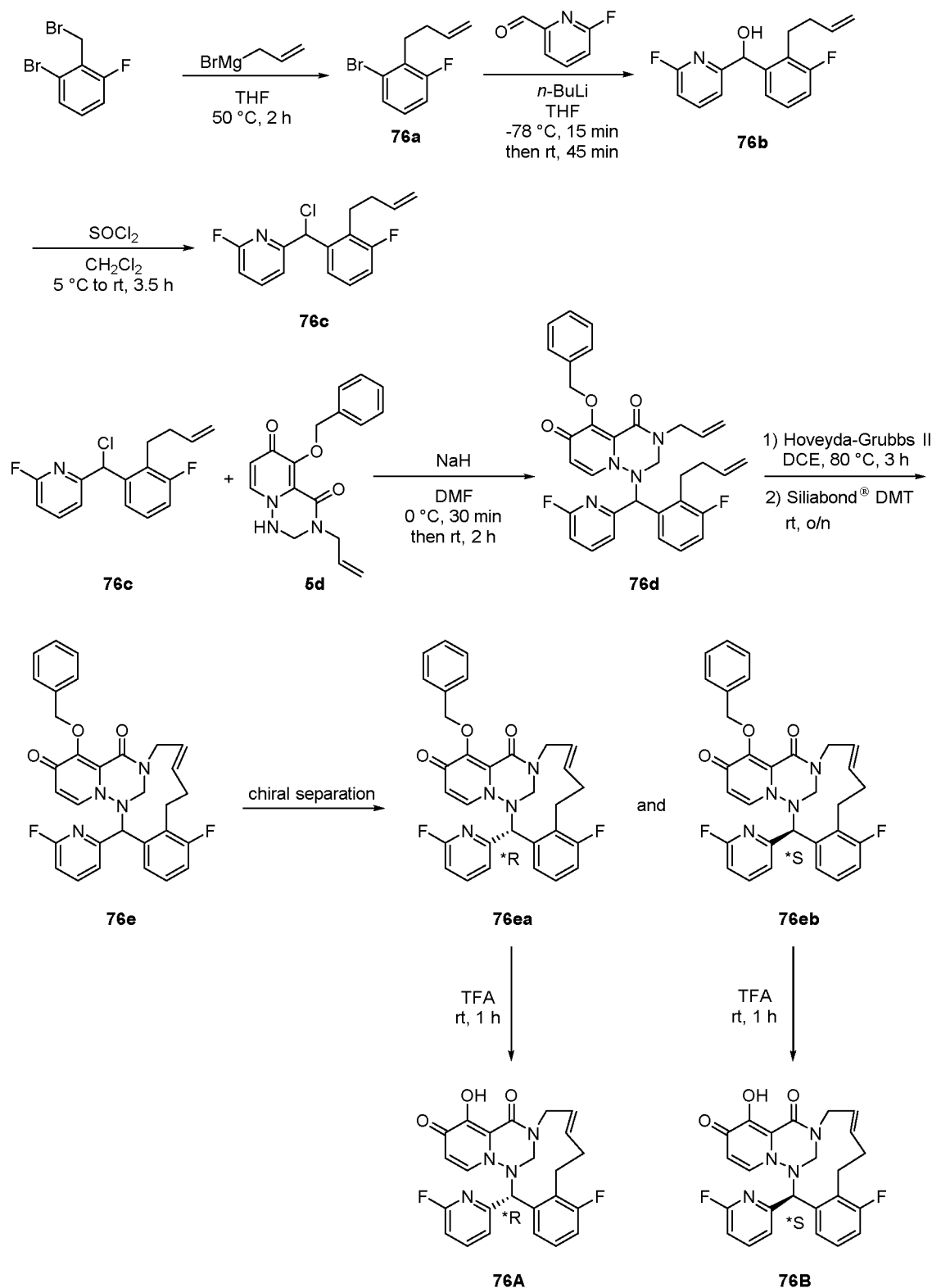
(18**S,Z*)-4-chloro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **75B**, 226 mg) was obtained using the procedure described for compound **28A**.

Compound 75B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.08 (br d, *J*=7.6 Hz, 1H), 7.57 (dd, *J*=7.9, 0.9 Hz, 1H), 7.42 (t, *J*=7.9 Hz, 1H), 7.00 - 7.27 (m, 6H), 6.27 (br s, 1H), 5.90 (br s, 1H), 5.49
5 (d, *J*=7.6 Hz, 1H), 5.31 (br s, 1H), 5.17 (d, *J*=13.6 Hz, 1H), 4.76 - 4.88 (m, 2H), 4.32 (br d, *J*=13.9 Hz, 2H), 3.22 (br dd, *J*=14.2, 7.6 Hz, 1H).
LC/MS (method LC-C): Rt 2.74 min, MH⁺ 450
[α]_D²⁰: -623.19 ° (c 0.276, DMF)

- 10 Example 76: synthesis of (16**R,E*)-12-fluoro-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **76A**), (16**S,E*)-12-fluoro-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **76B**)

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Synthesis of intermediate 76a:

Under nitrogen atmosphere, allylmagnesium bromide (1.0 M, 28.0 mL, 28 mmol) was added slowly to a solution of 1-bromo-2-(bromomethyl)-3-fluorobenzene [CAS 1548-81-8] (5.00 g, 18.7 mmol) in anhydrous THF (46 mL) at 0°C . The reaction mixture was

stirred at 50 °C for 2 h. The reaction was quenched by the addition of a 10% aqueous solution of NH₄Cl. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered and evaporated in vacuo to afford 1-bromo-2-(but-3-en-1-yl)-3-fluorobenzene (intermediate **76a**, 4.00 g).

5

Synthesis of intermediate 76b:

(2-(but-3-en-1-yl)-3-fluorophenyl)(6-fluoropyridin-2-yl)methanol (intermediate **76b**, 1.1 g) was obtained using the procedure described for intermediate **23a**.

10 **Synthesis of intermediate 76c:**

2-((2-(but-3-en-1-yl)-3-fluorophenyl)chloromethyl)-6-fluoropyridine (intermediate **76c**, 1.2 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 76d:

15 3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)-3-fluorophenyl)(6-fluoropyridin-2-yl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **76d**, 0.37 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 76e:

20 (*E*)-4-(benzyloxy)-12-fluoro-16-(6-fluoropyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **76e**, 176 mg) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: Chiralcel OD-H 5µm 250x21.2mm, Mobile phase: 60% CO₂, 40% MeOH) to afford the first eluted enantiomer

25 **76ea** (70 mg) and the second eluted enantiomer **76eb** (72 mg).

Synthesis of compound 76A:

(16**R,E*)-4-(benzyloxy)-12-fluoro-16-(6-fluoropyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **76A**, 41 mg) was obtained using the procedure described for compound **1**.

30

Compound 76A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.88 (d, *J*=7.9 Hz, 1H), 7.79 (q, *J*=7.9 Hz, 1H), 7.41 - 7.48 (m, 1H), 7.33 (dd, *J*=7.6, 1.9 Hz, 1H), 7.16 (t, *J*=9.1 Hz, 1H), 7.08 (d, *J*=7.9 Hz, 1H), 6.97 - 7.02 (m, 1H), 5.94 (br dt, *J*=15.1, 7.9 Hz, 1H), 5.50 (d, *J*=7.9 Hz, 1H), 5.42 - 5.48 (m, 1H), 5.24 (s, 1H), 5.07 (d, *J*=13.9 Hz, 1H), 4.65 (dd, *J*=14.2, 5.0 Hz, 1H), 4.18 (d, *J*=13.6 Hz, 1H), 3.03 (dd, *J*=13.9, 7.9 Hz, 1H), 2.74 (br d, *J*=13.9 Hz, 1H), 2.50 - 2.56 (m, 1H), 2.34 (br t, *J*=12.9 Hz, 1H), 1.91 - 2.00 (m, 1H).

35

LC/MS (method LC-C): Rt 2.74 min, MH⁺ 451

[α]_D²⁰: +556.00 ° (c 0.150, DMF)

Synthesis of compound 76B:

- 5 16**S,E*)-12-fluoro-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **76B**, 40 mg) was obtained using the procedure described for compound **1**.

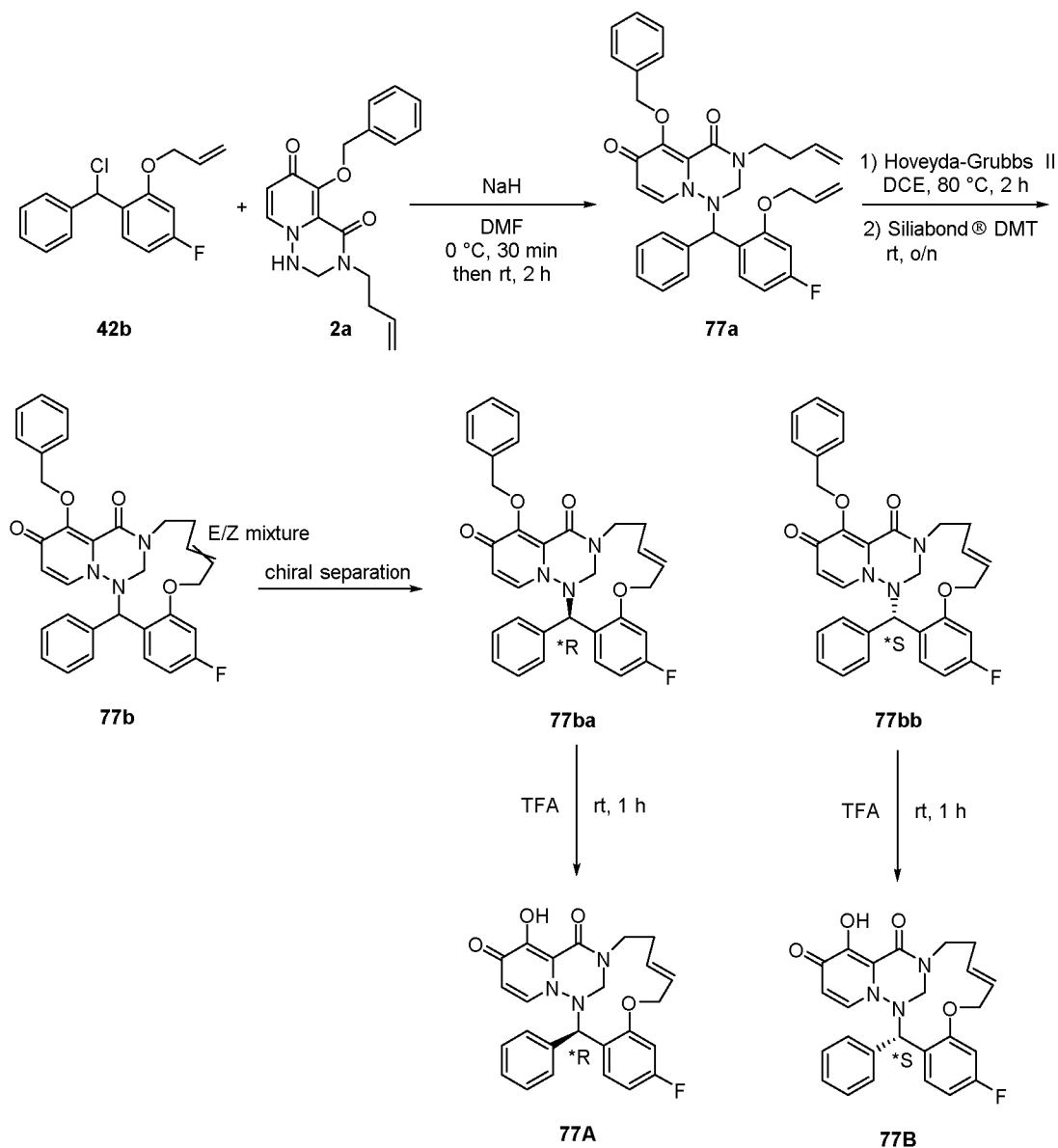
Compound 76B:

- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 (d, *J*=7.9 Hz, 1H), 7.87 (q, *J*=8.1 Hz, 1H), 7.48 - 7.55 (m, 1H), 7.41 (dd, *J*=7.3, 1.9 Hz, 1H), 7.24 (t, *J*=9.0 Hz, 1H), 7.16 (d, *J*=7.9 Hz, 1H), 7.07 (dd, *J*=8.2, 2.2 Hz, 1H), 6.02 (dt, *J*=15.5, 7.8 Hz, 1H), 5.57 (d, *J*=7.6 Hz, 1H), 5.49 - 5.56 (m, 1H), 5.32 (s, 1H), 5.15 (d, *J*=13.6 Hz, 1H), 4.73 (dd, *J*=13.9, 5.0 Hz, 1H), 4.26 (d, *J*=13.6 Hz, 1H), 3.10 (dd, *J*=13.9, 7.9 Hz, 1H), 2.81 (br d, *J*=13.6 Hz, 1H),
15 2.57 - 2.63 (m, 1H), 2.41 (br t, *J*=12.8 Hz, 1H), 1.98 - 2.08 (m, 1H).

LC/MS (method LC-C): Rt 2.74 min, MH⁺ 451

[α]_D²⁰: -550.00 ° (c 0.166, DMF)

- Example 77: synthesis of (*7E*,19**R*)-3-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-
20 6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (Compound **77A**), (*7E*,19**R*)-3-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (Compound **77B**)



Synthesis of intermediate 77a:

1-((2-(allyloxy)-4-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate 77a, 3.6 g) was obtained using the procedure described for intermediate 2d.

Synthesis of intermediate 77b:

(*E/Z*)-15-(benzyloxy)-34-fluoro-2-phenyl-12,13,14,16-tetrahydro-1*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (intermediate 77b, mixture of *Z* and *E* isomers, 760 mg) was obtained using the procedure described for intermediate 1f. Crude intermediate 77b (3.27 g) was purified by flash chromatography over silica gel (20-45 μm, 120 g, CH₂Cl₂/MeOH from 99/1 to 92/8).

The residue (1.47 g) was purified a second time by flash chromatography over silica gel (20-45 μ m, 40 g, toluene/*i*-PrOH 95/5) to afford intermediate **77b**.

The isomers were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 μ m 250*30mm, Mobile phase: 75% CO₂, 25% EtOH) to afford the first eluted enantiomer **77ba** (253 mg) and the second eluted enantiomer **77b** (271 mg). The enantiomer **77bb** was re-purified via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 μ m 250*30mm, Mobile phase: 77% CO₂, 23% EtOH) to deliver 234 mg of pure enantiomer **77bb**.

Synthesis of compound **77A**:

- 10 (7*E*,19**R*)-3-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (compound **77A**, 137 mg) was obtained using the procedure for compound **1**.

Compound **77A**:

- 15 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.72 (br s, 1H), 8.04 (dd, *J*=8.8, 6.9 Hz, 1H), 6.99 - 7.30 (m, 8H), 5.99 (ddd, *J*=15.5, 9.9, 5.2 Hz, 1H), 5.86 (s, 1H), 5.57 (ddd, *J*=15.2, 10.2, 4.6 Hz, 1H), 5.38 (d, *J*=7.6 Hz, 1H), 5.03 (d, *J*=12.9 Hz, 1H), 4.70 (dd, *J*=11.8, 5.2 Hz, 1H), 4.27 (d, *J*=12.9 Hz, 1H), 4.23 (dd, *J*=12.0, 10.4 Hz, 1H), 3.78 (br dt, *J*=13.2, 3.5 Hz, 1H), 2.84 - 2.94 (m, 1H), 2.78 - 2.86 (m, 1H), 2.24 (br d, *J*=12.9 Hz, 1H).
- 20 LC/MS (method LC-C): Rt 2.71 min, MH⁺ 448
[α]_D²⁰: +420.73 ° (c 0.193, DMF)
Chiral HPLC (method HPLC-B): Rt 4.30 min, chiral purity 100%

Synthesis of compound **77B**:

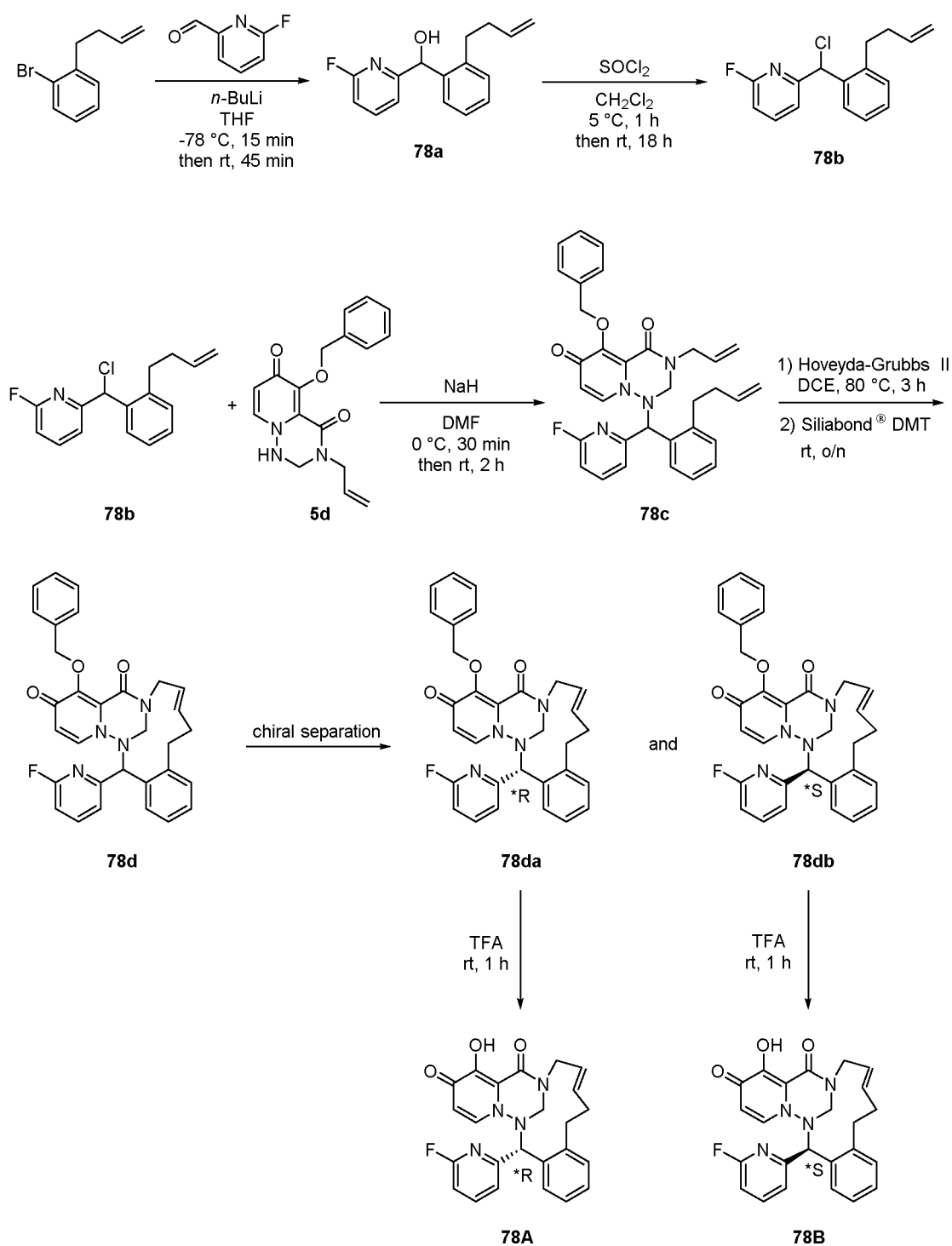
- 25 (7*E*,19**S*)-3-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (compound **77B**, 102 mg) was obtained using the procedure for compound **1**.

Compound **77B**:

- 30 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.73 (br s, 1H), 8.04 (dd, *J*=8.5, 7.3 Hz, 1H), 7.00 - 7.26 (m, 8H), 5.99 (ddd, *J*=15.4, 9.9, 5.2 Hz, 1H), 5.86 (s, 1H), 5.57 (ddd, *J*=14.8, 10.1, 4.4 Hz, 1H), 5.38 (d, *J*=7.6 Hz, 1H), 5.03 (d, *J*=12.9 Hz, 1H), 4.70 (dd, *J*=11.8, 5.2 Hz, 1H), 4.27 (d, *J*=12.9 Hz, 1H), 4.24 (dd, *J*=11.7, 10.1 Hz, 1H), 3.78 (dt, *J*=13.2, 3.5 Hz, 1H), 2.86 - 2.94 (m, 1H), 2.77 - 2.86 (m, 1H), 2.23 (br d, *J*=12.9 Hz, 1H).
- 35 LC/MS (method LC-C): Rt 2.72 min, MH⁺ 478
[α]_D²⁰: -411.24 ° (c 0.169, DMF)
Chiral HPLC (method HPLC-B): Rt 5.38 min, chiral purity 99.3%

Example 78: synthesis of (16**R,E*)-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (Compound **78A**), (16**S,E*)-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione

5 (Compound **78B**)



Synthesis of intermediate 78a:

(2-(but-3-en-1-yl)phenyl)(6-fluoropyridin-2-yl)methanol (intermediate **78a**, 1.6 g) was obtained using the procedure described for intermediate **23a**.

5 Synthesis of intermediate 78b:

2-((2-(but-3-en-1-yl)phenyl)chloromethyl)-6-fluoropyridine (intermediate **78b**, 1.7 g) was obtained using the procedure described for intermediate **5a**.

Synthesis of intermediate 78c:

- 10 3-allyl-5-(benzyloxy)-1-((2-(but-3-en-1-yl)phenyl)(6-fluoropyridin-2-yl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **78c**, 1.07 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 78d:

- 15 (*E*)-4-(benzyloxy)-16-(6-fluoropyridin-2-yl)-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (intermediate **78d**, 0.50 g) was obtained using the procedure described for intermediate **1f**.

- The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250*30mm, Mobile phase: 60% CO₂, 40% EtOH) to afford the first eluted
20 enantiomer **78da** (197 mg) and the second eluted enantiomer **78db** (211 mg).

Synthesis of compound 78A:

- (16**R,E*)-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **78A**,
25 132 mg) was obtained using the procedure described for compound **1**.

Compound 78A:

- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.08 (dd, *J*=7.9, 0.9 Hz, 1H), 7.85 (q, *J*=8.2 Hz, 1H), 7.30 - 7.48 (m, 3H), 7.23 (dd, *J*=7.6, 0.9 Hz, 1H), 7.17 (d, *J*=7.9 Hz, 1H), 7.04
30 (dd, *J*=8.0, 2.4 Hz, 1H), 5.90 - 5.98 (m, 1H), 5.59 (d, *J*=7.6 Hz, 1H), 5.43 - 5.51 (m, 1H), 5.31 (s, 1H), 5.13 (d, *J*=13.9 Hz, 1H), 4.70 (dd, *J*=14.2, 5.0 Hz, 1H), 4.27 (d, *J*=13.6 Hz, 1H), 3.09 (dd, *J*=14.0, 8.0 Hz, 1H), 2.52 - 2.67 (m, 3H), 1.98 - 2.07 (m, 1H).

LC/MS (method LC-C): Rt 2.67 min, MH⁺ 433

- 35 [α]_D²⁰: -591.76 ° (c 0.182, DMF)

Chiral HPLC (method HPLC-B): Rt 5.43 min, chiral purity 100%

Synthesis of compound 78B:

(16*S,*E*)-16-(6-fluoropyridin-2-yl)-4-hydroxy-7,10,11,16-tetrahydro-6,17-methanobenzo[*k*]pyrido[1,2-*b*][1,2,5]triazacyclotridecine-3,5-dione (compound **78B**, 134 mg) was obtained using the procedure described for compound **1**.

5

Compound 78B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.08 (d, *J*=7.9 Hz, 1H), 7.85 (q, *J*=8.1 Hz, 1H), 7.30 - 7.48 (m, 3H), 7.23 (d, *J*=7.6 Hz, 1H), 7.17 (d, *J*=7.6 Hz, 1H), 7.04 (dd, *J*=8.2, 2.2 Hz, 1H), 5.89 - 5.99 (m, 1H), 5.57 (d, *J*=7.6 Hz, 1H), 5.42 - 5.51 (m, 1H), 5.31 (s, 1H), 5.13 (d, *J*=13.6 Hz, 1H), 4.70 (dd, *J*=14.0, 5.2 Hz, 1H), 4.26 (d, *J*=13.9 Hz, 1H), 3.09 (dd, *J*=13.9, 7.9 Hz, 1H), 2.52 - 2.67 (m, 3H), 1.98 - 2.07 (m, 1H).

LC/MS (method LC-C): Rt 2.67 min, MH⁺ 433

[α]_D²⁰: +598.59 ° (c 0.142, DMF)

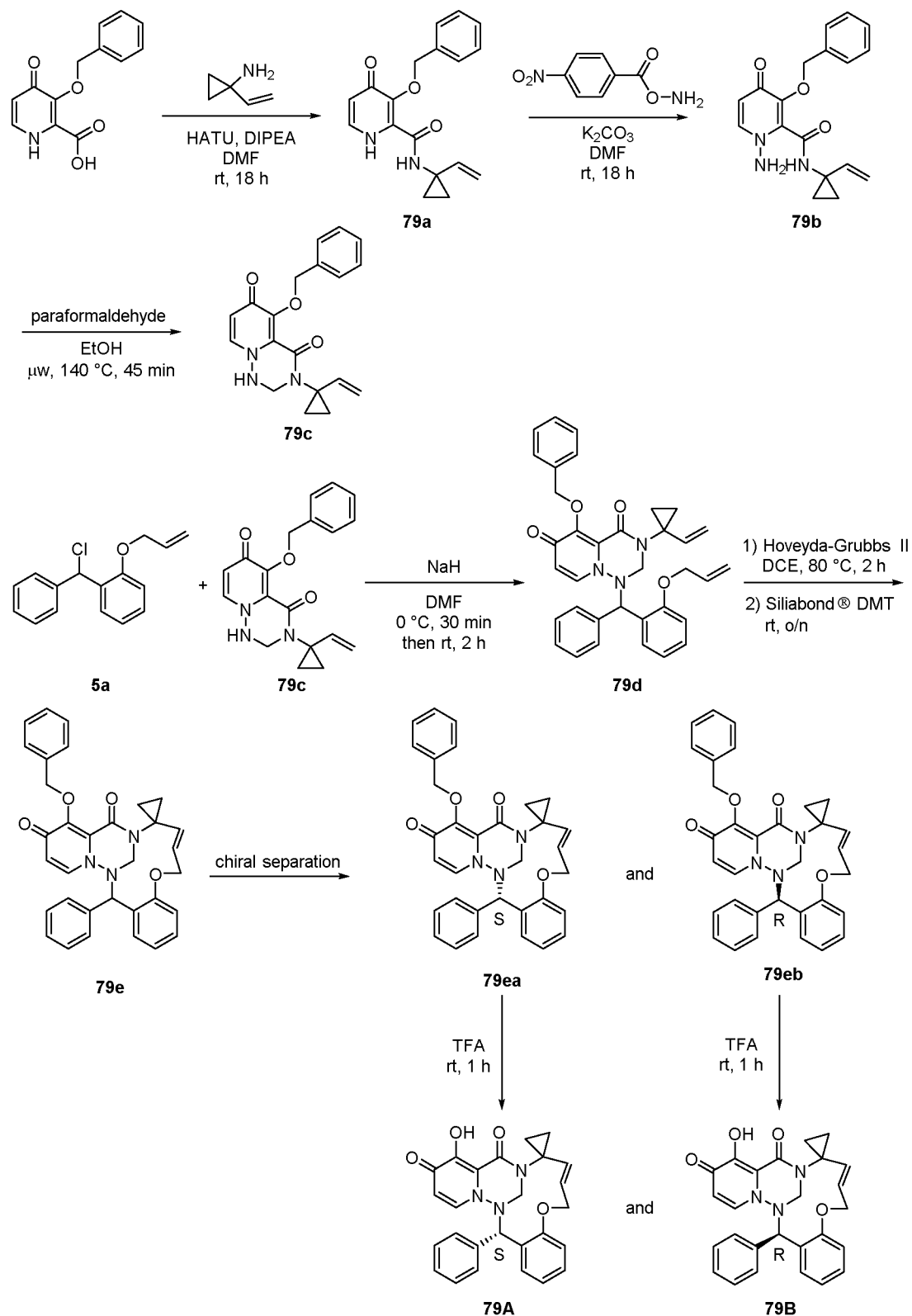
Chiral HPLC (method HPLC-B): Rt 6.04 min, chiral purity 100%

15

Example 79: synthesis of (18'*S*,*E*)-12'-hydroxy-18'-phenyl-6'*H*,18'*H*-spiro[cyclopropane-1,9'-[10,17]methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **79A**), (18'*R*,*E*)-12'-hydroxy-18'-phenyl-6'*H*,18'*H*-spiro[cyclopropane-1,9'-[10,17]methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **79B**)

20

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Synthesis of intermediate 79a:

3-(benzyloxy)-4-oxo-N-(1-vinylcyclopropyl)-1,4-dihydropyridine-2-carboxamide (intermediate **79a**, 3.0 g) was obtained using the procedure described for intermediate

Synthesis of intermediate 79b:

1-amino-3-(benzyloxy)-4-oxo-N-(1-vinylcyclopropyl)-1,4-dihydropyridine-2-carboxamide (intermediate **79b**, 1.1 g) was obtained using the procedure described for intermediate **1b**. Crude intermediate **79b** was purified by trituration in CH₂Cl₂.

Synthesis of intermediate 79c:

In a microwave vial, a mixture of intermediate **79b** (1.10 g, 3.38 mmol) and paraformaldehyde (0.10 g, 3.38 mmol) in EtOH (12 mL) was stirred at 140 °C using a single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 45 min. The reaction mixture was filtered to afford a first fraction of 5-(benzyloxy)-3-(1-vinylcyclopropyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **79c**, 0.35 g) and the filtrate was concentrated in vacuo to deliver a second fraction of intermediate **79c** (0.63 g).

Synthesis of intermediate 79d:

1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-(1-vinylcyclopropyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **79d**, 0.49 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 79e:

(*E*)-12'-(benzyloxy)-18'-phenyl-6'*H*,18'*H*-spiro[cyclopropane-1,9'-[10,17]methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (intermediate **79e**, 0.18 g) was obtained using the procedure described for intermediate **1f**.

The enantiomers were separated via chiral SFC (Stationary phase: AS 5µm 250*20mm, Mobile phase: 45% CO₂, 55% EtOH) to afford the first eluted enantiomer **79ea** (73 mg) and the second eluted enantiomer **79eb** (74 mg).

Synthesis of compound 79A:

(18'*S,E*)-12'-hydroxy-18'-phenyl-6'*H*,18'*H*-spiro[cyclopropane-1,9'-[10,17]methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (compound **79A**, 40 mg) was obtained using the procedure described for compound **1**.

Compound 79A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.06 (dd, *J*=7.7, 1.4 Hz, 1H), 7.41 (td, *J*=7.8, 1.6 Hz, 1H), 7.35 (td, *J*=7.4, 1.0 Hz, 1H), 7.15 - 7.28 (m, 7H), 6.23 (br dt, *J*=15.2, 7.7 Hz, 1H), 5.78 (br d, *J*=15.1 Hz, 1H), 5.50 (d, *J*=7.6 Hz, 1H), 5.40 (s, 1H), 5.09 (d, *J*=13.6

Hz, 1H), 4.82 (dd, $J=11.0, 6.3$ Hz, 1H), 4.24 (br dd, $J=10.7, 9.1$ Hz, 1H), 4.18 (d, $J=13.6$ Hz, 1H), 1.45 - 1.52 (m, 1H), 1.12 - 1.19 (m, 1H), 0.82 - 0.88 (m, 1H), 0.67 - 0.75 (m, 1H).

LC/MS (method LC-C): Rt 2.71 min, MH^+ 442

5 $[\alpha]_D^{20}$: +569.7 ° (c 0.132, DMF)

Chiral HPLC (method HPLC-B): Rt 6.06 min, chiral purity 100%

Synthesis of compound 79B:

10 (18'*R,E*)-12'-hydroxy-18'-phenyl-6'*H*,18'*H*-spiro[cyclopropane-1,9'-
[10,17]methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione
(compound 79B, 40 mg) was obtained using the procedure described for compound 1.

Compound 79B:

15 ^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.06 (dd, $J=7.9, 1.6$ Hz, 1H), 7.41 (td, $J=7.6, 1.3$
Hz, 1H), 7.35 (td, $J=7.6, 1.0$ Hz, 1H), 7.16 - 7.28 (m, 7H), 6.18 - 6.27 (m, 1H), 5.78 (br
d, $J=15.8$ Hz, 1H), 5.50 (d, $J=7.6$ Hz, 1H), 5.40 (s, 1H), 5.09 (d, $J=13.6$ Hz, 1H), 4.82
(dd, $J=11.0, 6.3$ Hz, 1H), 4.24 (dd, $J=10.9, 9.0$ Hz, 1H), 4.18 (d, $J=13.6$ Hz, 1H), 1.45 -
1.52 (m, 1H), 1.12 - 1.19 (m, 1H), 0.82 - 0.88 (m, 1H), 0.68 - 0.74 (m, 1H).

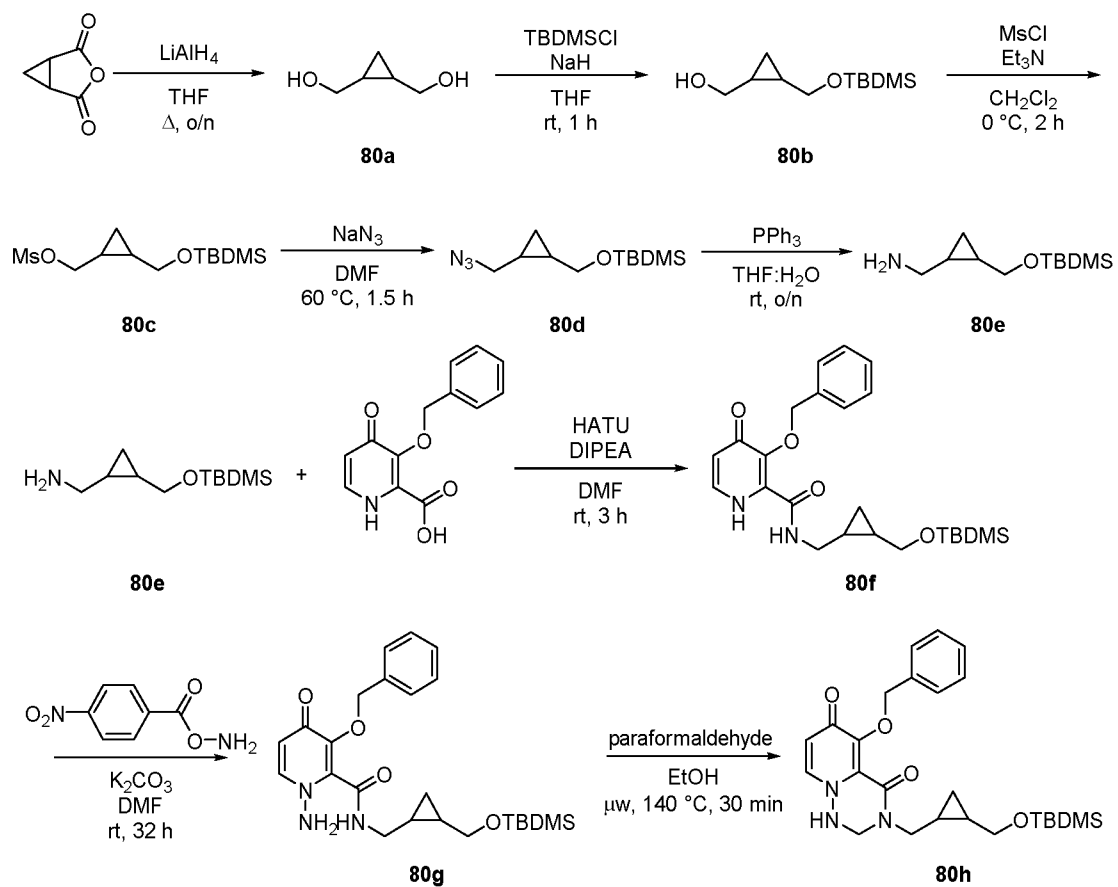
LC/MS (method LC-C): Rt 2.70 min, MH^+ 442

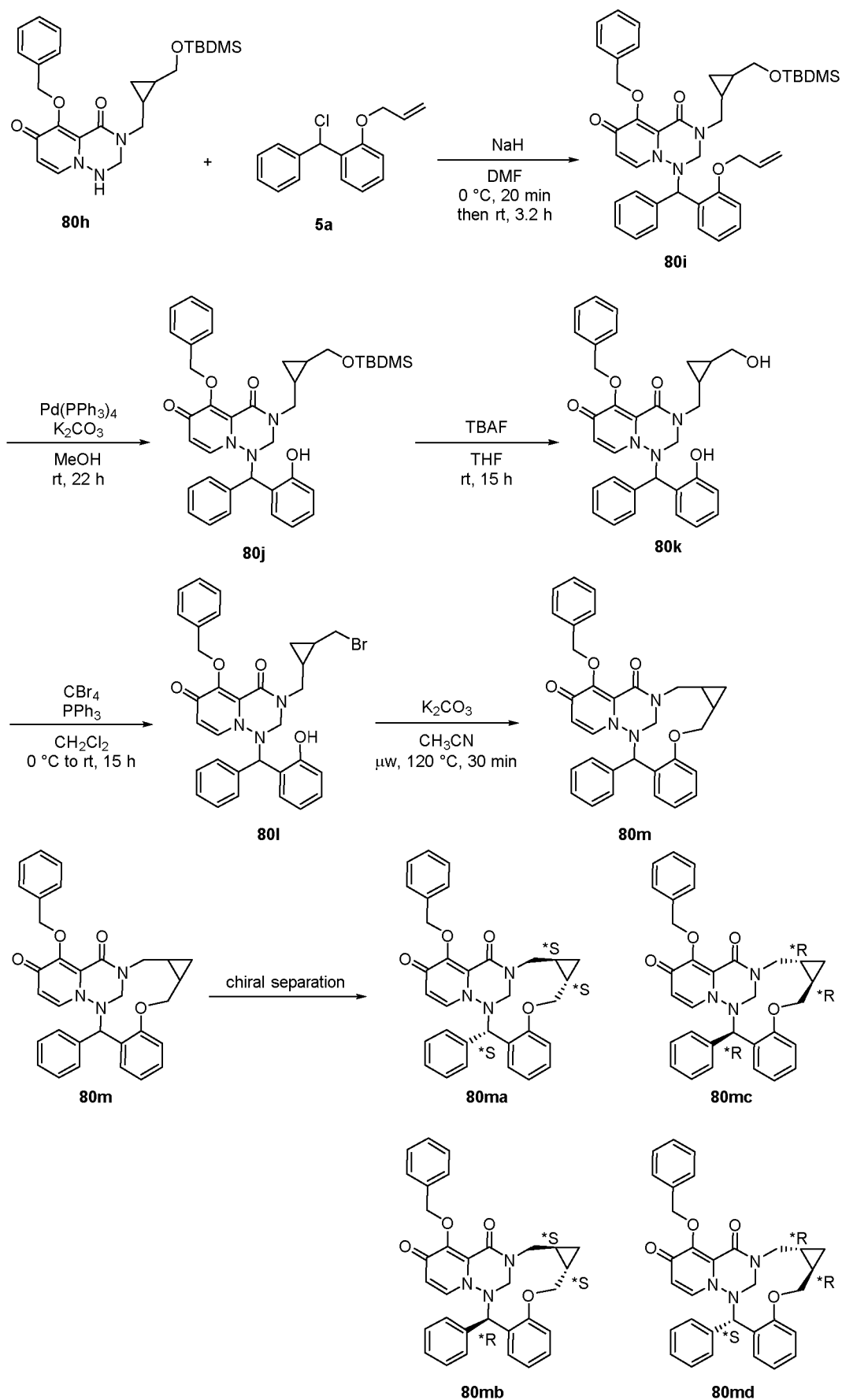
20 $[\alpha]_D^{20}$: -572.27 ° (c 0.154, DMF)

Chiral HPLC (method HPLC-B): Rt 6.68 min, chiral purity 100%

Example 80: synthesis of ((1a**S*,8**S*,17a**S*)-14-hydroxy-8-phenyl-1a,2,17,17a-
tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-
25 *f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound 80AA), (1a**R*,8**R*,17a**R*)-
14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-
methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-
dione (Compound 80BB), (1a**R*,8**S*,17a**R*)-14-hydroxy-8-phenyl-1a,2,17,17a-
tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-
30 *f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound 80AB) and
(1a**S*,8**R*,17a**S*)-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-
methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-
dione (Compound 80BA)

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Synthesis of intermediate 80a:

Under nitrogen atmosphere, to a solution of 3-oxabicyclo[3.1.0]hexane-2,4-dione [CAS 5617-74-3] (6.51g, 58.1 mmol) in anhydrous THF (195 mL) at 0 °C was added dropwise LiAlH₄ (1.0 M in THF, 87.1 mL, 87.1 mmol). The reaction mixture was stirred under reflux overnight. The reaction mixture was cooled to 0 °C and the reaction was quenched by the addition of Et₂O and water. The mixture was filtered over a pad of Celite[®]. The solid was suspended in THF and stirred under reflux for 16 h. The mixture was filtered and the solid was washed with hot THF (twice) and acetone. The filtrates were combined and concentrated in vacuo to afford cyclopropane-1,2-diyl dimethanol (intermediate **80a**, 5.93 g).

Synthesis of intermediate **80b**:

To a solution of intermediate **80a** (5.93 g, 58.1 mmol) in anhydrous THF (120 mL) at 0 °C under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 2.79 g, 69.7 mmol). The reaction mixture was stirred at rt for 45 min and TBDMSCl (8.75 g, 58.1 mmol) was added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with Et₂O and washed with a saturated aqueous solution of NH₄Cl and brine. The aqueous layer was back extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash chromatography over silica gel (220 g, petroleum ether/EtOAc from 100/0 to 0/100) afforded (2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methanol (intermediate **80b**, 9.81 g).

Synthesis of intermediate **80c**:

To a solution of intermediate **80b** (9.81 g, 45.3 mmol) in anhydrous CH₂Cl₂ (190 mL) at 0 °C under nitrogen atmosphere were added Et₃N (12.6 mL, 90.7 mmol) and methanesulfonyl chloride (4.2 mL, 54.4 mmol). The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with water and the mixture was extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to afford (2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl methanesulfonate (intermediate **80c**, 13.06 g).

Synthesis of intermediate **80d**:

To a solution of intermediate **80c** (13.0 g, 44.4 mmol) in anhydrous DMF (160 mL) was added NaN₃ (5.77 g, 88.7 mmol). The reaction mixture was stirred at 60 °C for 1.5 h. The reaction mixture was diluted with water and extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to afford

((2-(azidomethyl)cyclopropyl)methoxy)(*tert*-butyl)dimethylsilane (intermediate **80d**, 10.7 g).

Synthesis of intermediate 80e:

- 5 To a solution of intermediate **80d** (10.7 g, 44.4 mmol) in THF (90 mL) and H₂O (20 mL) was added PPh₃ (23.3 g, 88.7 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was partitioned between Et₂O and water. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash chromatography over silica gel (220 g,
10 CH₂Cl₂/MeOH from 95/5 to 70/30) and afforded (2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methanamine (intermediate **80e**, 6.83 g).

Synthesis of intermediate 80f:

- 3-(benzyloxy)-N-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl)-4-oxo-
15 1,4-dihydropyridine-2-carboxamide (intermediate **80f**, 7.66 g) was obtained using the procedure described for intermediate **5b**.

Synthesis of intermediate 80g:

- 1-amino-3-(benzyloxy)-N-((2-(((*tert*-
20 butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **80g**, 4.75 g) was obtained using the procedure described for intermediate **5c**.

Synthesis of intermediate 80h:

- 25 5-(benzyloxy)-3-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **80h**) was obtained using the procedure described for intermediate **5d**. Crude intermediate **80h** was combined with two other fractions (1.00 g, 2.19 mmol and 2.00 g, 4.37 mmol) and the mixture was purified by flash chromatography over silica gel (220 g, CH₂Cl₂/MeOH
30 from 100/0 to 90/10) to afford intermediate **80h** (3.58 g).

Synthesis of intermediate 80i:

- 1-((2-(allyloxy)phenyl)(phenyl)methyl)-5-(benzyloxy)-3-((2-(((*tert*-
butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-
35 *f*][1,2,4]triazine-4,6-dione (intermediate **80i**, 2.02 g) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 80j:

Intermediate **80i** (2.02 g, 2.93 mmol) was dissolved in MeOH (33 mL) under nitrogen atmosphere. Pd(PPh₃)₄ (338 mg, 293 μmol) was added. The mixture was stirred for 10 min at rt and K₂CO₃ (1.21 g, 8.78 mmol) was added. The reaction mixture was stirred at
5 rt for 22 h. The reaction mixture was concentrated in vacuo. The residue was taken up in CH₂Cl₂ and washed with water and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash column chromatography (80 g, CH₂Cl₂/MeOH from 100/0 to 96/4) to afford 5-(benzyloxy)-3-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl)-1-((2-
10 hydroxyphenyl)(phenyl)methyl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **80j**, 1.54 g).

Synthesis of intermediate 80k:

Intermediate **80j** (1.55 g, 2.37 mmol) was dissolved in anhydrous THF (25 mL) under
15 nitrogen atmosphere. TBAF (1.0 M in THF, 2.84 mL, 2.84 mmol) was added and the reaction mixture was stirred at rt for 15 h. The reaction mixture was diluted with MeOH and concentrated in vacuo. Purification was carried out by flash column chromatography (40 g, CH₂Cl₂/MeOH from 100/0 to 94/6) to afford 5-(benzyloxy)-3-((2-(hydroxymethyl)cyclopropyl)methyl)-1-((2-hydroxyphenyl)(phenyl)methyl)-2,3-
20 dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **80k**, 1.1 g).

Synthesis of intermediate 80l:

Intermediate **80k** (501 mg, 932 μmol) was dissolved in anhydrous CH₂Cl₂ (15 mL) under nitrogen atmosphere. The solution was cooled to 0 °C and PPh₃ (407 mg, 1.86 mmol)
25 was added. The mixture was stirred for 15 min and CBr₄ (618 mg, 1.86 mmol) was added. The reaction mixture was stirred at rt for 15 h. The reaction mixture was concentrated in vacuo. Purification was carried out by flash column chromatography (80 g, CH₂Cl₂/MeOH from 100/0 to 96/4) to afford 5-(benzyloxy)-3-((2-(bromomethyl)cyclopropyl)methyl)-1-((2-hydroxyphenyl)(phenyl)methyl)-2,3-dihydro-
30 1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **80l**, 538 mg).

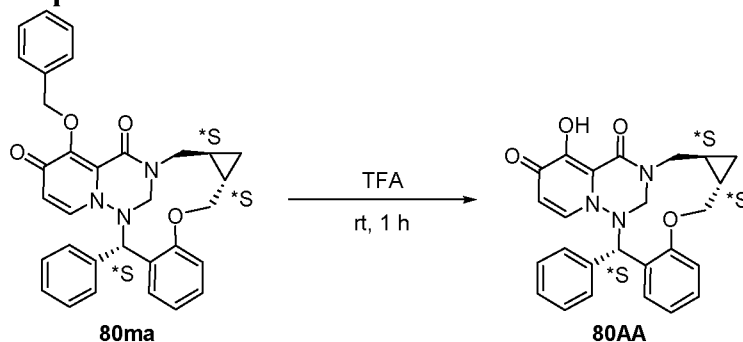
Synthesis of intermediate 80m

Intermediate **80l** (538 mg, 896 μmol) was dissolved in anhydrous CH₃CN (20 mL) under nitrogen atmosphere. K₂CO₃ (248 mg, 1.79 mmol) was added and the reaction mixture
35 was stirred at 120 °C under microwave irradiation for 30 min. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash column chromatography (40 g, CH₂Cl₂/MeOH from 100/0 to 96/4). The residue was triturated

with Et₂O to afford 14-(benzyloxy)-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (intermediate **80m**, 260 mg) as a mixture of diastereoisomers.

The diastereoisomers were separated via chiral SFC (Stationary phase: CHIRALPAK AS-H 5μm 250*20mm, Mobile phase: 75% CO₂, 25% MeOH) to afford two fractions: fraction A (intermediates **80mb** and **80mc**, 62 mg) and fraction B (intermediates **80ma** and **80md**, 37 mg). Fraction A was purified via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5μm 250*21.2mm, Mobile phase: 75% CO₂, 25% MeOH) to afford intermediate **80mb** (29 mg) and intermediate **80mc** (17 mg). Fraction B was purified via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5μm 250*21.2mm, Mobile phase: 70% CO₂, 30% MeOH) to afford intermediate **80md** (20 mg) and intermediate **80ma** (13 mg).

Synthesis of compound **80AA**:



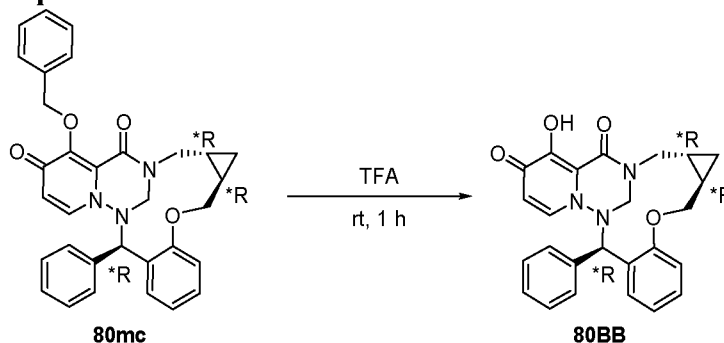
(1a**S*,8**S*,17a**S*)-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (compound **80AA**, 4 mg) was obtained using the procedure described for compound **1**.

Compound **80AA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.21 (dd, *J*=7.9, 1.6 Hz, 1H), 7.38 - 7.43 (m, 2H), 7.33 - 7.36 (m, 1H), 7.29 (t, *J*=7.4 Hz, 1H), 7.21 - 7.26 (m, 2H), 7.16 - 7.20 (m, 3H), 6.08 (s, 1H), 5.49 (d, *J*=7.9 Hz, 1H), 5.10 (d, *J*=13.6 Hz, 1H), 4.76 (dd, *J*=12.3, 3.5 Hz, 1H), 4.36 (dd, *J*=13.9, 2.5 Hz, 1H), 4.29 (d, *J*=13.2 Hz, 1H), 2.16 (dd, *J*=13.9, 11.0 Hz, 1H), 1.27 - 1.35 (m, 1H), 0.98 - 1.06 (m, 1H), 0.55 (dt, *J*=9.0, 4.7 Hz, 1H), 0.35 (dt, *J*=9.1, 4.8 Hz, 1H).

LC/MS (method LC-C): Rt 2.62 min, MH⁺ 430

Chiral HPLC (method HPLC-B): Rt 5.73 min, chiral purity 98%

Synthesis of compound 80BB:

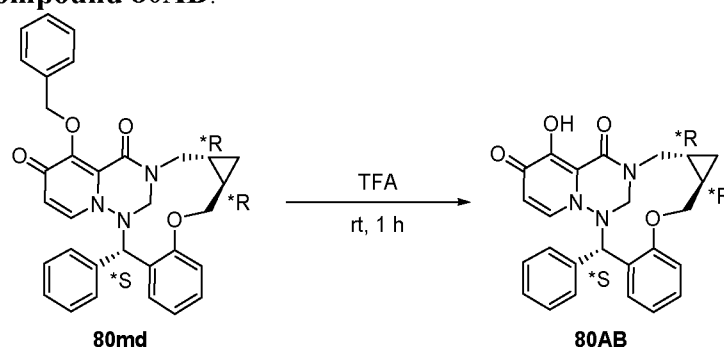
(1a^{*R},8^{*R},17a^{*R})-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (compound **80BB**, 9 mg) was obtained using the procedure described for compound **1**.

Compound 80BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.21 (dd, *J*=7.9, 1.3 Hz, 1H), 7.38 - 7.43 (m, 2H), 7.33 - 7.36 (m, 1H), 7.29 (t, *J*=7.4 Hz, 1H), 7.21 - 7.25 (m, 2H), 7.17 - 7.21 (m, 3H), 6.08 (s, 1H), 5.50 (d, *J*=7.6 Hz, 1H), 5.10 (d, *J*=13.6 Hz, 1H), 4.76 (dd, *J*=12.3, 3.5 Hz, 1H), 4.36 (dd, *J*=14.0, 2.4 Hz, 1H), 4.29 (d, *J*=13.6 Hz, 1H), 2.16 (dd, *J*=13.9, 11.3 Hz, 1H), 1.27 - 1.35 (m, 1H), 0.98 - 1.06 (m, 1H), 0.55 (dt, *J*=8.9, 4.5 Hz, 1H), 0.35 (dt, *J*=9.1, 4.8 Hz, 1H) (mixture of isomers 65/35)

LC/MS (method LC-C): Rt 2.60 min, MH⁺ 430 (presence of an isomer)

Chiral HPLC (method HPLC-B): Rt 5.18 min, chiral purity 100%

Synthesis of compound 80AB:

(1a^{*R},8^{*S},17a^{*R})-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (compound **80AB**, 10 mg) was obtained using the procedure described for compound **1**.

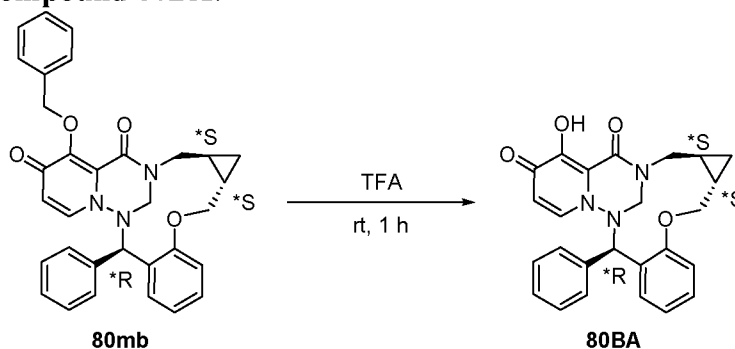
Compound 80AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.03 (dd, *J*=7.7, 1.4 Hz, 1H), 7.20 - 7.37 (m, 8H), 7.07 (d, *J*=8.2 Hz, 1H), 5.99 (s, 1H), 5.51 (d, *J*=7.6 Hz, 1H), 5.05 (d, *J*=13.6 Hz, 1H), 4.84 (dd, *J*=12.8, 4.6 Hz, 1H), 4.47 (d, *J*=13.6 Hz, 1H), 3.52 (br dd, *J*=14.3, 10.2 Hz, 1H), 3.39 (br s, 1H), 3.18 (br dd, *J*=14.7, 4.9 Hz, 1H), 1.32 - 1.40 (m, 1H), 0.64 - 0.73 (m, 2H), 0.50 - 0.56 (m, 1H).

LC/MS (method LC-C): Rt 2.63 min, MH⁺ 430

[α]_D²⁰: -302.75 ° (c 0.109, DMF)

Chiral HPLC (method HPLC-B): Rt 7.10 min, chiral purity 100%

Synthesis of compound 80BA:

(1a**S*,8**R*,17a**S*)-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1*H*,8*H*-9,16-methanobenzo[*b*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (compound **80BA**, 16 mg) was obtained using the procedure described for compound **1**.

Compound 80BA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.03 (dd, *J*=7.6, 1.6 Hz, 1H), 7.20 - 7.44 (m, 8H), 7.07 (d, *J*=8.2 Hz, 1H), 5.99 (s, 1H), 5.51 (d, *J*=7.9 Hz, 1H), 5.05 (d, *J*=13.2 Hz, 1H), 4.84 (dd, *J*=12.9, 4.7 Hz, 1H), 4.47 (d, *J*=13.6 Hz, 1H), 3.52 (br dd, *J*=14.3, 10.2 Hz, 1H), 3.39 (br s, 1H), 3.18 (br dd, *J*=14.7, 4.9 Hz, 1H), 1.31 - 1.40 (m, 1H), 0.64 - 0.74 (m, 2H), 0.49 - 0.57 (m, 1H).

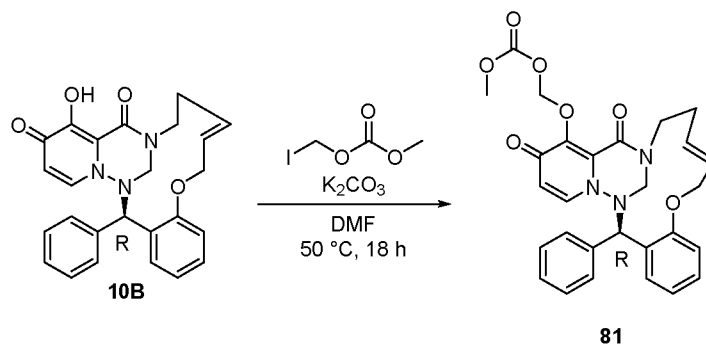
LC/MS (method LC-C): Rt 2.63 min, MH⁺ 430

[α]_D²⁰: +260.00 ° (c 0.14, DMF)

Chiral HPLC (method HPLC-B): Rt 5.41 min, chiral purity 100%

Example 81: synthesis of (((2*R*,*E*)-14,16-dioxo-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-*f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-en-15-yl)oxy)methyl methyl carbonate (Compound **81**)

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**Synthesis of compound 81:**

(((2*R,E*)-14,16-dioxo-2-phenyl-12,13,14,16-tetrahydro-11*H*-4-oxa-1(1,3)-pyrido[2,1-
 5 *f*][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-en-15-yl)oxy)methyl methyl
 carbonate (compound **81**, 332 mg) was obtained using the procedure described for
 compound **62**. After purification by flash chromatography the residue was triturated in
 Et₂O.

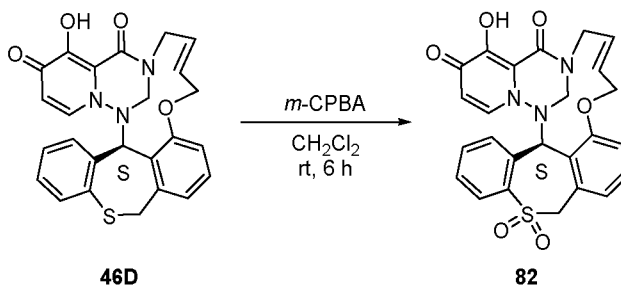
Compound 81:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.01 (dd, *J*=7.7, 1.4 Hz, 1H), 7.41 (td, *J*=7.7, 1.6
 Hz, 1H), 7.32 (t, *J*=7.3 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 7.12 - 7.20 (m, 4H), 7.08 (br s,
 1H), 6.01 (s, 1H), 5.89 (ddd, *J*=15.3, 9.9, 4.7 Hz, 1H), 5.64 (d, *J*=6.6 Hz, 1H), 5.59 (d,
J=3.8 Hz, 1H), 5.57 (d, *J*=4.7 Hz, 1H), 5.49 (br ddd, *J*=15.2, 10.3, 4.4 Hz, 1H), 5.03 (d,
 15 *J*=12.9 Hz, 1H), 4.72 (dd, *J*=11.8, 5.2 Hz, 1H), 4.21 (d, *J*=12.9 Hz, 1H), 4.16 (dd, *J*=11.8,
 10.3 Hz, 1H), 3.79 (s, 3H), 3.69 (br dt, *J*=13.5, 3.5 Hz, 1H), 2.89 - 3.00 (m, 1H), 2.78 -
 2.86 (m, 1H), 2.17 (br d, *J*=12.3 Hz, 1H).

LC/MS (method LC-C): Rt 2.73 min, MH⁺ 518

[α]_D²⁰: -406.33 ° (c 0.156, DMF)

Example 82: synthesis of (17*aS,E*)-12-hydroxy-2,6,9,17*a*-tetrahydro-3,4-
 (epi^{prop}[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-
 20 *f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione 1,1-dioxide (Compound **82**)



25

Synthesis of compound 82:

At 0 °C, *m*-CPBA (26.4 mg, 153 μmol) was added to a solution of intermediate **46D** (32.0 mg, 69.6 μmol) in CH₂Cl₂ (1 mL). The reaction mixture was stirred at rt for 6 h. The reaction mixture was diluted with CH₂Cl₂ and washed with water. The organic phase was dried over MgSO₄, filtered and the solvent was evaporated in vacuo. Purification was carried out by flash chromatography over silica gel (30 μm, 24 g, CH₂Cl₂/MeOH from 99/1 to 97/3) The pure fractions were collected and evaporated to dryness. The product was freeze-dried (water/CH₃CN, 4/1) to give (17a*S,E*)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi)prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione 1,1-dioxide (compound **82**, 13 mg).

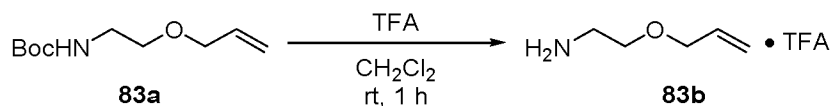
Compound 82:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.40 (br s, 1H), 7.85 (dd, *J*=7.9, 0.9 Hz, 1H), 7.57 - 7.63 (m, 1H), 7.49 (t, *J*=7.9 Hz, 1H), 7.41 (td, *J*=7.6, 1.3 Hz, 1H), 7.36 (dd, *J*=12.1, 7.7 Hz, 2H), 7.13 (d, *J*=7.9 Hz, 1H), 7.10 (d, *J*=7.3 Hz, 1H), 6.57 (d, *J*=14.5 Hz, 1H), 6.29 (dt, *J*=15.6, 7.6 Hz, 1H), 5.83 - 5.93 (m, 1H), 5.51 - 5.56 (m, 2H), 5.19 (d, *J*=13.9 Hz, 1H), 4.98 (d, *J*=14.5 Hz, 1H), 4.85 (dd, *J*=11.0, 6.3 Hz, 1H), 4.75 (dd, *J*=14.2, 4.1 Hz, 1H), 4.47 (br t, *J*=10.1 Hz, 1H), 4.20 (d, *J*=13.9 Hz, 1H), 3.15 (dd, *J*=14.3, 7.7 Hz, 1H).

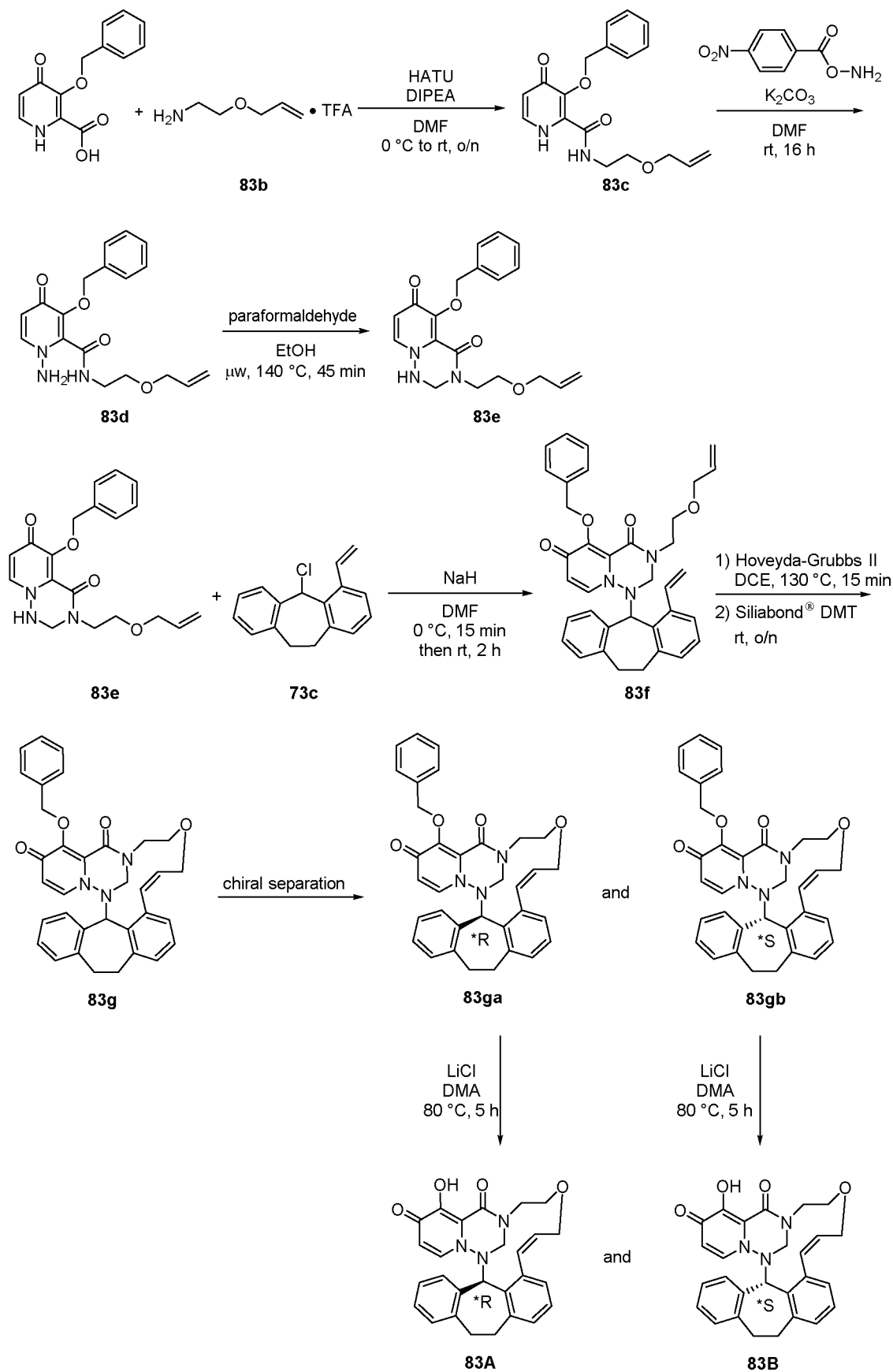
LC/MS (method LC-C): Rt 2.12 min, MH⁺ 492

[α]_D²⁰: -445.5 ° (c 0.200, DMF)

Example 83: synthesis of (13*Z*,23*b***R*)-6-hydroxy-9,10,12,18,19,23*b*-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-*c*][9,2,3,6]benzoxatriazacyclotetradecine-5,7-dione (Compound **83A**), (13*Z*,23*b***S*)-6-hydroxy-9,10,12,18,19,23*b*-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-*c*][9,2,3,6]benzoxatriazacyclotetradecine-5,7-dione (Compound **83B**)



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Synthesis of intermediate 83b:

To a solution of intermediate **83a** [CAS 441752-75-6] (29.6 g, 147 mmol) in CH₂Cl₂ (75 mL) was added TFA (75 mL) portionwise. The reaction mixture was stirred at rt for 1 h. The mixture was concentrated in vacuo and co-evaporated with toluene. Purification was carried out by flash column chromatography on silica gel (220 g, CH₂Cl₂/(CH₂Cl₂/MeOH/NH₄OH 70/29/1) from 100/0 to 0/100) to afford 2-(prop-2-en-1-yloxy)ethan-1-amine, trifluoroacetic acid (intermediate **83b**, 29.6 g).

Synthesis of intermediate 83c:

N-(2-(allyloxy)ethyl)-3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **83c**, 5.3 g) was obtained using the procedure described for intermediate **5b**.

Synthesis of intermediate 83d:

N-(2-(allyloxy)ethyl)-1-amino-3-(benzyloxy)-4-oxo-1,4-dihydropyridine-2-carboxamide (intermediate **83d**, 3.1 g) was obtained using the procedure described for intermediate **1b**.

Synthesis of intermediate 83e:

3-(2-(allyloxy)ethyl)-5-(benzyloxy)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **83e**, 290 mg) was obtained using the procedure described for intermediate **73f**.

Synthesis of intermediate 83f:

3-(2-(allyloxy)ethyl)-5-(benzyloxy)-1-(4-vinyl-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **83f**, 170 mg) was obtained using the procedure described for intermediate **2d**.

Synthesis of intermediate 83g:

(13*Z*)-6-(benzyloxy)-9,10,12,18,19,23*b*-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-*c*][9,2,3,6]benzoxatriazacyclotetradecine-5,7-dione (crude intermediate **83g**) was obtained using the procedure described for intermediate **59d**.

Crude intermediate **83g** was purified by flash chromatography over silica gel (40 g, CH₂Cl₂/MeOH from 100/0 to 98/2). A second purification was performed by flash chromatography C18 (40 μm, 45 g, H₂O/MeOH from 70/30 to 0/100). The residue was

finally purified via achiral SFC (Stationary phase: AMINO 5 μ m 150*30 mm, Mobile phase: 80% CO₂, 20% MeOH) to afford intermediate **83g** (105 mg).

The enantiomers were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5 μ m 250*21.2mm, Mobile phase: 45% CO₂, 55% MeOH) to afford the first eluted enantiomer

5 **83ga** (44 mg) and the second eluted enantiomer **83gb** (46 mg).

Synthesis of compound **83A**:

((13Z,23b*R)-6-hydroxy-9,10,12,18,19,23b-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-

10 *c*][9,2,3,6]benzoxatriazacyclotetradecine-5,7-dione (compound **83A**, 19 mg) was obtained using the procedure described for compound **28A**.

Compound **83A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.67 (br s, 1H), 7.24 - 7.31 (m, 2H), 7.16 - 7.22
15 (m, 1H), 7.08 - 7.13 (m, 2H), 7.06 (d, *J*=7.6 Hz, 1H), 6.90 (t, *J*=7.3 Hz, 1H), 6.63 - 6.74 (m, 2H), 6.37 (dt, *J*=11.3, 6.4 Hz, 1H), 5.38 - 5.43 (m, 2H), 4.94 (d, *J*=12.7 Hz, 1H), 4.58 (td, *J*=14.0, 5.3 Hz, 1H), 4.47 (ddd, *J*=13.0, 7.2, 1.5 Hz, 1H), 4.30 (d, *J*=12.7 Hz, 1H), 3.89 (br d, *J*=13.6 Hz, 1H), 3.62 - 3.74 (m, 3H), 3.55 (br d, *J*=17.4 Hz, 1H), 2.88 - 2.98 (m, 1H), 2.71 - 2.80 (m, 2H).

20 LC/MS (method LC-C): Rt 2.88 min, MH⁺ 456
[α]_D²⁰: +227.12 ° (c 0.236, DMF)

Synthesis of compound **83B**:

((13Z,23b*S)-6-hydroxy-9,10,12,18,19,23b-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-

25 *c*][9,2,3,6]benzoxatriazacyclotetradecine-5,7-dione (compound **83B**, 23 mg) was obtained using the procedure described for compound **28A**.

Compound **83B**:

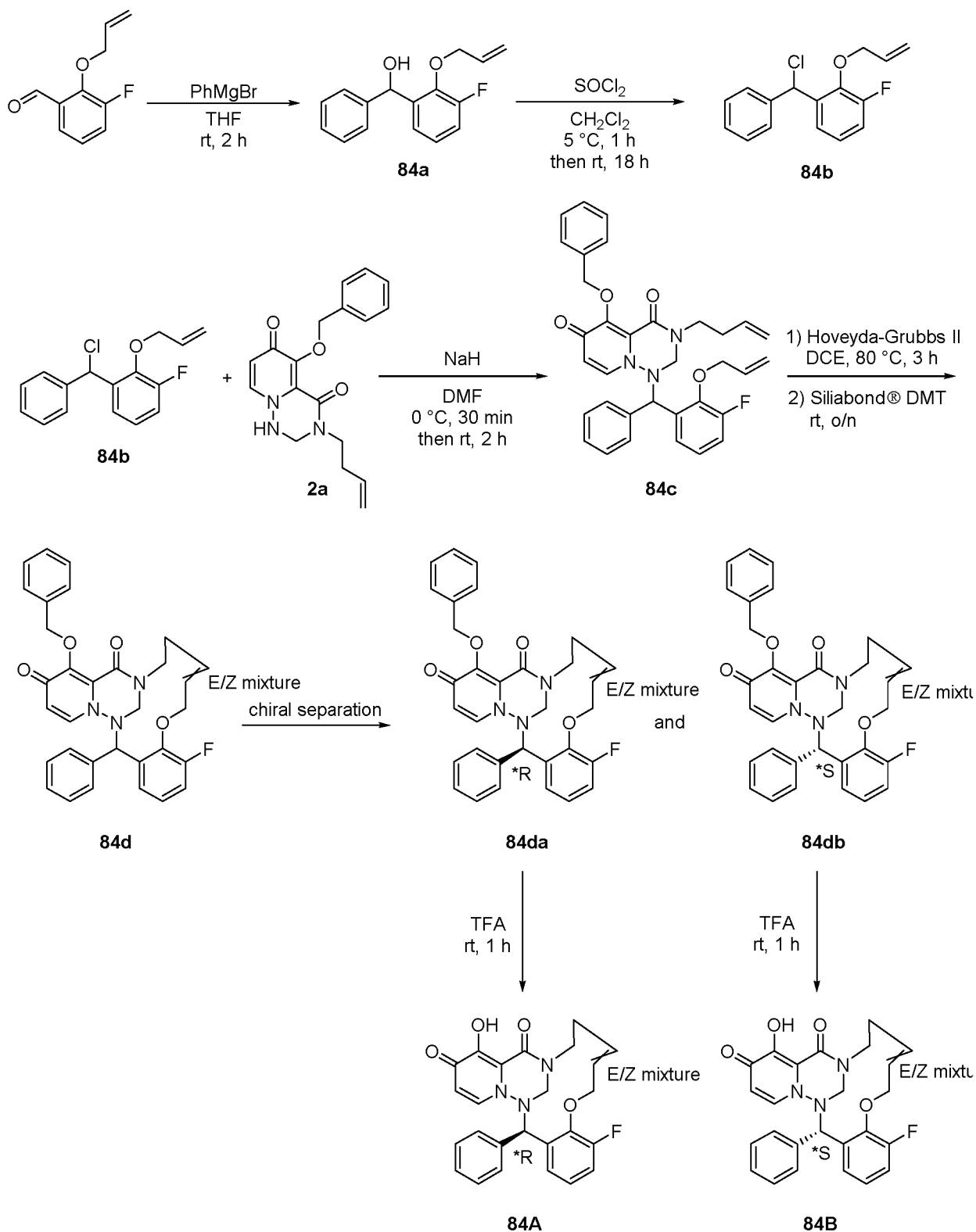
30 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.67 (br s, 1H), 7.25 - 7.31 (m, 2H), 7.17 - 7.22 (m, 1H), 7.08 - 7.12 (m, 2H), 7.06 (d, *J*=7.6 Hz, 1H), 6.90 (t, *J*=7.6 Hz, 1H), 6.64 - 6.72 (m, 2H), 6.37 (dt, *J*=10.9, 6.5 Hz, 1H), 5.38 - 5.44 (m, 2H), 4.94 (d, *J*=12.6 Hz, 1H), 4.58 (br td, *J*=13.9, 5.0 Hz, 1H), 4.47 (ddd, *J*=13.0, 7.3, 1.1 Hz, 1H), 4.30 (d, *J*=12.6 Hz, 1H), 3.89 (br d, *J*=14.8 Hz, 1H), 3.62 - 3.75 (m, 3H), 3.55 (br d, *J*=17.0 Hz, 1H), 2.88 - 2.98
35 (m, 1H), 2.71 - 2.80 (m, 2H).

LC/MS (method LC-C): Rt 2.88 min, MH⁺ 456
[α]_D²⁰: -220.43 ° (c 0.230, DMF)

Example 84: synthesis of (19**R*, *E/Z*)-4-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (Compound **84A**), (19**S*, *E/Z*)-4-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (Compound **84B**)

5

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**Synthesis of intermediate 84a:**

(2-(allyloxy)-3-fluorophenyl)(phenyl)methanol (intermediate **84a**, 2.8 g) was obtained using the procedure described for intermediate **2b**. Crude intermediate **84a** was purified by flash chromatography over silica gel (30 μm , 80 g, heptane/EtOAc 90/10).

Synthesis of intermediate 84b:

2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene (intermediate **84b**, 3.0 g) was obtained using the procedure described for intermediate **5a**.

5 Synthesis of intermediate 84c:

1-((2-(allyloxy)-3-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **84c**, 3.3 g) was obtained using the procedure described for intermediate **2d**.

10 Synthesis of intermediate 84d:

(*E/Z*)13-(benzyloxy)-4-fluoro-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (intermediate **84d**, mixture of *Z* and *E* isomers, 2.4 g) was obtained using the procedure described for intermediate **1f**.

15 The isomers were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 53% CO₂, 47% (MeOH/CH₂Cl₂ 90/10)) to afford the first eluted enantiomer **84da** (1.05 g) and the second eluted enantiomer **84db** (1.03 g).

Synthesis of compound 84A:

20 (19**R*, *E/Z*)-4-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (compound **84A**, mixture of *Z* and *E* isomers 9/91, 530 mg) was obtained using the procedure described for compound **1**.

25 Compound 84A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.73 (br s, 1H), 7.87 (d, *J*=7.9 Hz, 1H), 7.30 - 7.41 (m, 2H), 6.92 - 7.22 (m, 6H), 6.07 (br ddd, *J*=15.3, 10.2, 4.7 Hz, 1H), 5.98 (s, 1H), 5.63 (br ddd, *J*=15.1, 10.3, 4.3 Hz, 1H), 5.41 (d, *J*=7.6 Hz, 1H), 5.09 (d, *J*=12.9 Hz, 1H), 4.73 (dd, *J*=12.0, 5.0 Hz, 1H), 4.33 (d, *J*=12.9 Hz, 1H), 4.04 (t, *J*=10.9 Hz, 1H), 3.81 (dt, *J*=13.2, 3.3 Hz, 1H), 2.79 - 2.97 (m, 2H), 2.26 (br d, *J*=12.3 Hz, 1H).

LC/MS (method LC-C): Rt 2.69 min, MH⁺ 448

[α]_D²⁰: +425.62 ° (c 0.121, DMF)

Chiral HPLC (method HPLC-B): Rt 4.94 min, chiral purity 100%

35 Synthesis of compound 84B:

(19**S*, *E/Z*)-4-fluoro-13-hydroxy-19-phenyl-9,10-dihydro-6*H*,19*H*-11,18-methanopyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-12,14-dione (compound

84B, mixture of *Z* and *E* isomers 8/92, 560 mg) was obtained using the procedure described for compound **1**.

Compound 84B:

5 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.70 (br s, 1 H), 7.87 (br d, *J*=7.9 Hz, 1H), 7.30 - 7.41 (m, 2H), 6.93 - 7.23 (m, 6H), 6.07 (br ddd, *J*=15.0, 10.1, 4.9 Hz, 1H), 5.98 (s, 1H), 5.63 (ddd, *J*=15.1, 10.2, 4.3 Hz, 1H), 5.41 (d, *J*=7.9 Hz, 1H), 5.09 (d, *J*=13.2 Hz, 1H), 4.73 (br dd, *J*=12.0, 5.0 Hz, 1H), 4.33 (d, *J*=12.9 Hz, 1H), 4.04 (br t, *J*=11.0 Hz, 1H), 3.81 (br d, *J*=13.6 Hz, 1H), 2.87 - 2.97 (m, 1H), 2.79 - 2.88 (m, 1H), 2.26 (br d, *J*=13.2
10 Hz, 1H).

LC/MS (method LC-C): Rt 2.69 min, MH⁺ 448

[α]_D²⁰: -422.5 ° (c 0.160, DMF)

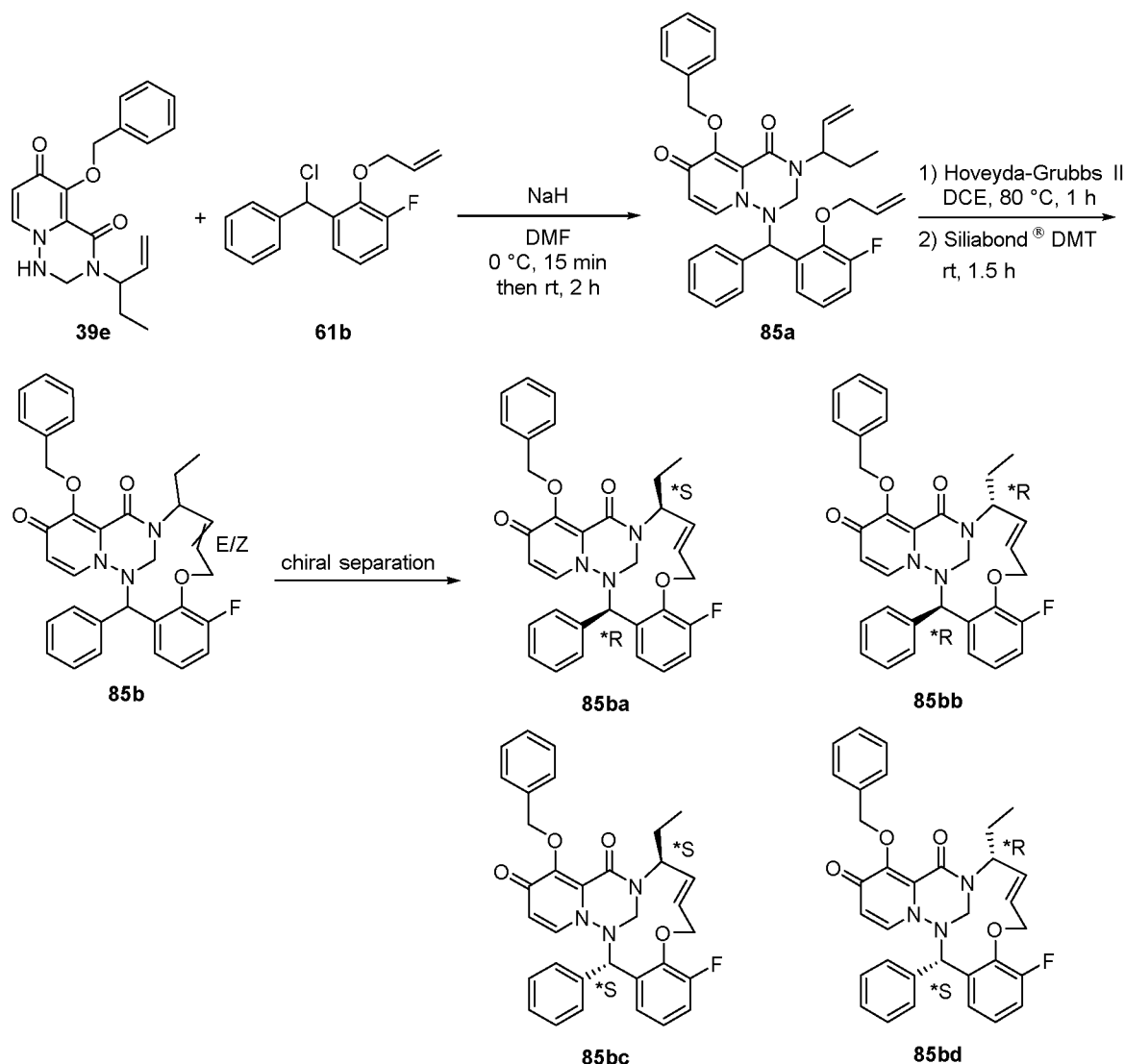
Chiral HPLC (method HPLC-B): Rt 6.06 min, chiral purity 93.6%

15

Example 85: synthesis of (9^{*}*S*,18^{*}*R,E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **85AA**), (9^{*}*R*,18^{*}*S,E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-

20 *f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **85BB**), (9^{*}*R*,18^{*}*R,E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **85AB**) and (9^{*}*S*,18^{*}*S,E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-

25 11,13-dione (Compound **85BA**)



Synthesis of intermediate **85a**:

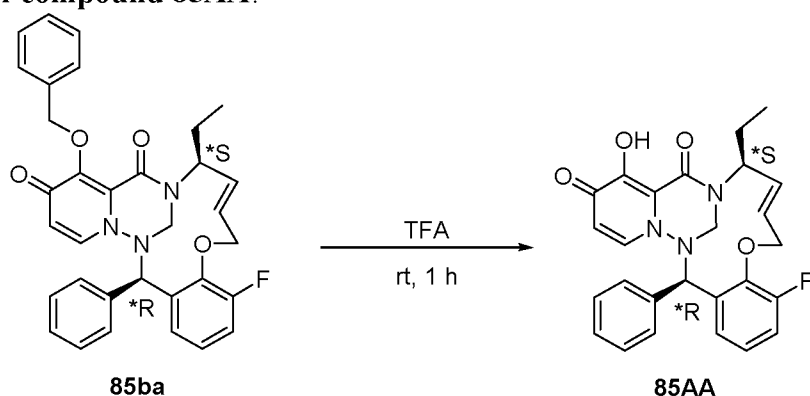
Under nitrogen atmosphere, to solution of intermediate **39e** (844 mg, 2.49 mmol) in anhydrous DMF (20 mL) at -20 °C was added NaH (60% dispersion in mineral oil, 169 mg, 4.23 mmol). The mixture was stirred for 5 min at this temperature and a solution of intermediate **61b** (1.03 g, 3.72 mmol) in anhydrous DMF (20 mL) was added dropwise. The reaction mixture was allowed to warm to 0 °C and stirred for 7 h. The reaction mixture was diluted with EtOAc and the reaction was quenched by the careful addition of a saturated aqueous solution of NH₄Cl. The layers were separated and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with a saturated aqueous solution of NH₄Cl and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash chromatography over silica gel (40 g, CH₂Cl₂/MeOH from 100/0 to 95/5). A second purification was performed over silica gel (40 g, petroleum ether/EtOAc from 100/0 to 0/100) to afford 1-((2-(allyloxy)-

3-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-3-(pent-1-en-3-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **85a**, 815 mg).

Synthesis of intermediate **85b**:

- 5 (*E/Z*)-12-(benzyloxy)-9-ethyl-4-fluoro-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (crude intermediate **85b**) was obtained using the procedure described for intermediate **1f**. Crude intermediate **85b** was purified by flash chromatography over silica gel (80 g, CH₂Cl₂/MeOH from 100/0 to 95/5). A second purification was performed by reverse
- 10 flash chromatography on silica C18 (30 g, H₂O/MeOH from 70/30 to 0/100) to afford intermediate **85b** (358 mg). The product was combined with another fraction (352 mg) and the mixture was purified again by flash chromatography over silica gel (80 g, toluene/*i*-PrOH from 100/0 to 90/10) to afford intermediate **85b** (518 mg). Purification by chiral SFC (Stationary phase: CHIRALPAK IC 5μm 250*30mm, Mobile
- 15 phase: 50% CO₂, 50% MeOH) to afford intermediate **85b** (2 fractions of 77 mg and 194 mg) and intermediate **85ba** (127 mg). The fraction **85b** (194 mg) was purified via chiral SFC (Stationary phase: CHIRALPAK IC 5μm 250*30mm, Mobile phase: 50% CO₂, 50% MeOH) to afford intermediate **85bd** (111 mg) and intermediate **85bb** (58 mg).
- 20 The second fraction **85b** (77 mg) was purified via chiral SFC (Stationary phase: CHIRACEL OJ-H 5μm 250*30mm, Mobile phase: 80% CO₂, 20% MeOH) to afford intermediate **85bc** (64 mg).

Synthesis of compound **85AA**:



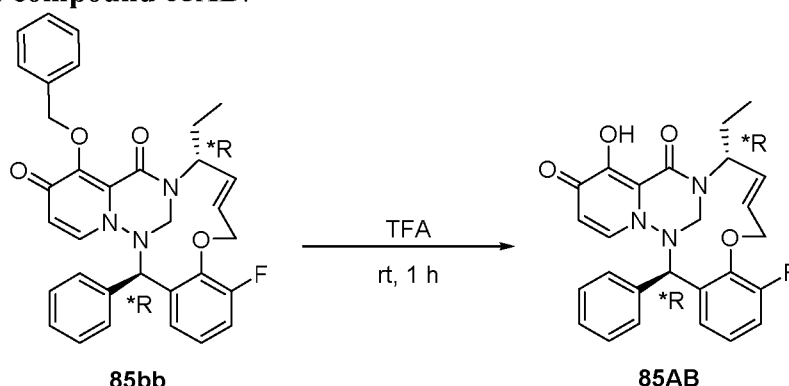
(9**S*,18**R,E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **85AA**, 50 mg) was obtained using the procedure described for compound **1**.

Compound 85AA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (br d, *J*=7.9 Hz, 1H), 7.32 - 7.45 (m, 2H), 7.04 - 7.26 (m, 6H), 6.37 (br ddd, *J*=15.3, 10.2, 5.0 Hz, 1H), 5.53 (dd, *J*=15.1, 5.0 Hz, 1H), 5.48 (d, *J*=7.6 Hz, 1H), 5.21 (s, 1H), 5.18 (q, *J*=7.6 Hz, 1H), 5.06 (d, *J*=13.6 Hz, 1H), 4.88 (br dd, *J*=11.3, 5.4 Hz, 1H), 4.22 (d, *J*=13.6 Hz, 1H), 3.99 (br t, *J*=10.7 Hz, 1H), 1.53 (dq, *J*=14.3, 7.0 Hz, 1H), 1.39 - 1.49 (m, 1H), 0.83 (t, *J*=7.3 Hz, 3H).

LC/MS (method LC-C): Rt 2.89 min, MH⁺ 462

[α]_D²⁰: -562.24 ° (c 0.241, DMF)

10 **Synthesis of compound 85AB:**

(9**R*,18**R,E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **85AB**, 24 mg) was obtained using the procedure described for compound **1**.

Compound 85AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.97 (br d, *J*=7.6 Hz, 1H), 7.36 - 7.43 (m, 1H), 7.30 - 7.36 (m, 2H), 7.14 - 7.21 (m, 3H), 7.10 (br s, 1H), 6.44 (br s, 1H), 5.89 (br s, 1H), 5.49 (d, *J*=7.6 Hz, 1H), 5.44 (s, 1H), 5.21 (d, *J*=13.9 Hz, 1H), 4.64 (br t, *J*=10.4 Hz, 1H), 4.54 (br s, 1H), 4.22 (d, *J*=14.2 Hz, 1H), 3.43 - 3.50 (m, 2H), 2.27 - 2.35 (m, 1H), 2.10 - 2.19 (m, 1H), 0.86 (t, *J*=7.4 Hz, 3H).

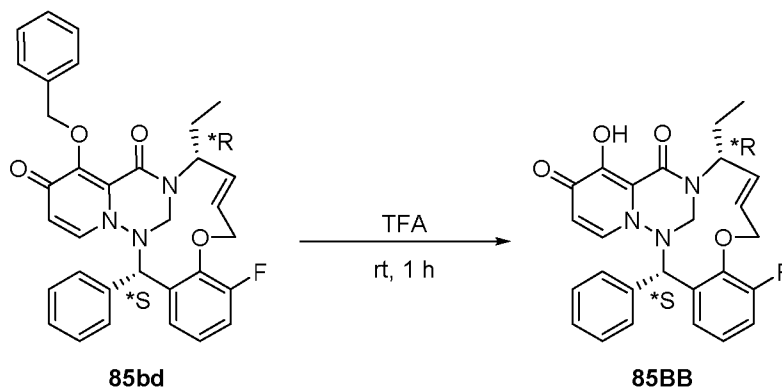
LC/MS (method LC-C): Rt 2.95 min, MH⁺ 462

[α]_D²⁰: -559.07 ° (c 0.281, DMF)

Chiral HPLC (method HPLC-B): Rt 8.45 min, chiral purity 100%

Synthesis of compound 85BB:

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(9**R*,18**S*,*E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **85BB**, 55 mg) was obtained using the procedure described for compound **1**.

5

Compound **85BB**:

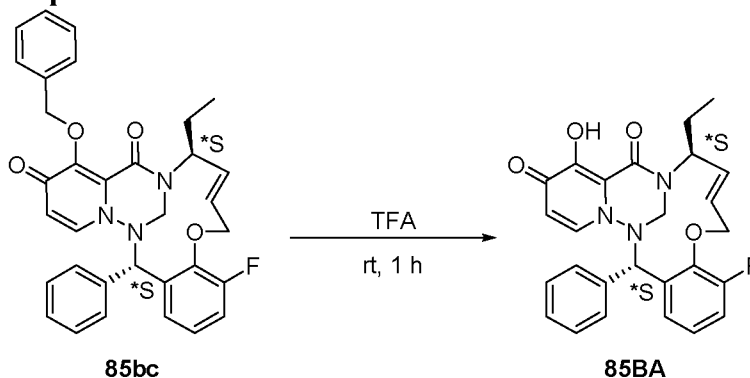
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (d, *J*=7.9 Hz, 1H), 7.41 (td, *J*=8.0, 5.5 Hz, 1H), 7.33 - 7.38 (m, 1H), 7.23 (d, *J*=7.6 Hz, 1H), 7.05 - 7.21 (m, 5H), 6.37 (br ddd, *J*=15.4, 10.2, 5.2 Hz, 1H), 5.52 (br dd, *J*=15.8, 6.3 Hz, 1H), 5.48 (d, *J*=7.6 Hz, 1H), 5.21 (s, 1H), 5.18 (q, *J*=7.5 Hz, 1H), 5.06 (d, *J*=13.6 Hz, 1H), 4.88 (dd, *J*=11.3, 5.4 Hz, 1H), 4.22 (d, *J*=13.2 Hz, 1H), 3.99 (br t, *J*=10.9 Hz, 1H), 1.49 - 1.58 (m, 1H), 1.39 - 1.49 (m, 1H), 0.83 (t, *J*=7.4 Hz, 3H).

LC/MS (method LC-C): Rt 2.89 min, MH⁺ 462

[α]_D²⁰: +600.42 ° (c 0.237, DMF)

15

Synthesis of compound **85BA**:



(9**S*,18**S*,*E*)-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **85BA**, 22 mg) was obtained using the procedure described for compound **1**.

20

Compound **85BA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.97 (br d, *J*=7.9 Hz, 1H), 7.36 - 7.42 (m, 1H), 7.29 - 7.36 (m, 2H), 7.14 - 7.20 (m, 3H), 7.09 (br s, 1H), 6.44 (br s, 1H), 5.88 (br s, 1H),

5.49 (d, $J=7.6$ Hz, 1H), 5.44 (s, 1H), 5.21 (d, $J=13.9$ Hz, 1H), 4.64 (br t, $J=10.4$ Hz, 1H), 4.54 (br s, 1H), 4.22 (d, $J=14.2$ Hz, 1H), 3.43 - 3.49 (m, 2H), 2.28 - 2.35 (m, 1H), 2.11 - 2.20 (m, 1H), 0.86 (t, $J=7.3$ Hz, 3H).

LC/MS (method LC-C): Rt 2.94 min, MH^+ 462

5 $[\alpha]_D^{20}$: +648.56 ° (c 0.243, DMF)

Chiral HPLC (method HPLC-B): Rt 5.74 min, chiral purity 100%

Example 86: synthesis of (13 *Z,23b *R)-6-hydroxy-10,11,12,18,19,23b-hexahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-

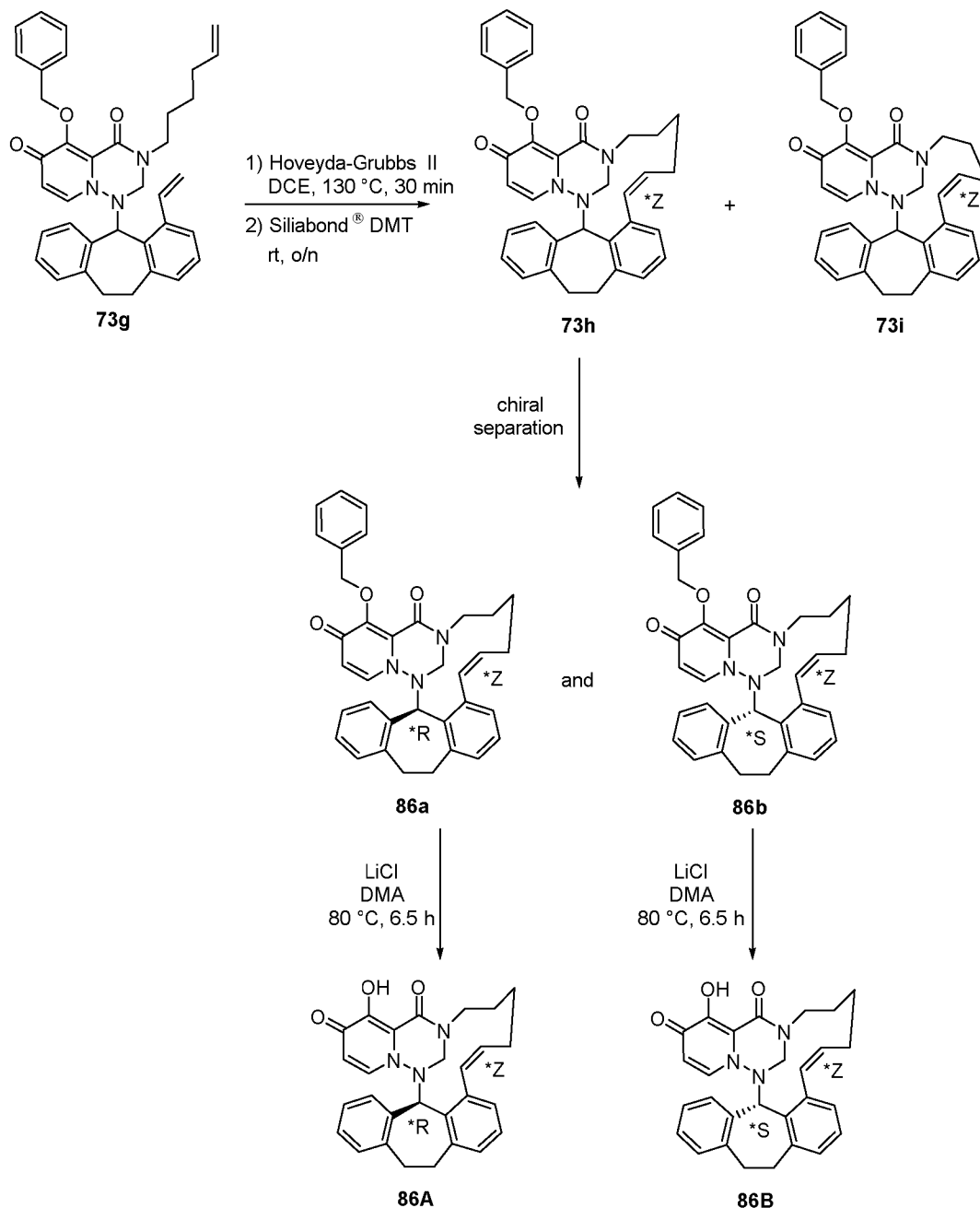
10 *c*][2,3,6]benzotriazacyclotetradecine-5,7-dione

(Compound **86A**), (13 *Z,23b *R)-6-hydroxy-10,11,12,18,19,23b-hexahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-

c][2,3,6]benzotriazacyclotetradecine-5,7-dione

(Compound **86B**)

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Synthesis of intermediates 73h and 73i:

A mixture of (13^{*}*Z*)-6-(benzyloxy)-10,11,12,18,19,23*b*-hexahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-

5 *c*][2,3,6]benzotriazacyclotetradecine-5,7-dione (intermediate 73h), (12^{*}*Z*)-6-(benzyloxy)-9,10,11,17,18,22*b*-hexahydro-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*pq*]pyrido[1,2-*c*][2,3,6]benzotriazacyclotridecine-5,7-dione (intermediate 73i) was obtained using the procedure described for intermediate 59d.

The crude mixture was purified by flash chromatography over silica gel (40 g, CH₂Cl₂/MeOH from 100/0 to 98/2) to afford intermediate 73h and intermediate 73i. The two products were independently purified by flash chromatography C18 (40 μm, 45 g,

H₂O/MeOH from 70/30 to 0/100) to give intermediate **73h** (510 mg) and intermediate **73i** (103 mg).

Intermediate **73h** was purified by flash chromatography over silica gel (15 μ m, 24 g, toluene/*i*-PrOH 94/6). The residue was purified via reverse phase (Stationary phase: YMC-actus Triart C18 10 μ m 30*150mm, mobile phase gradient: 0.2% aq.NH₄HCO₃/MeCN from 45/55 to 25/75) to afford intermediate **73h** (80 mg).

The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK AS-H 5 μ m 250*20mm, Mobile phase: 60% CO₂, 40% MeOH) to afford the first eluted enantiomer **86** (27 mg) and the second eluted enantiomer **86** (27 mg).

Synthesis of compound **86A**:

(13**Z*,23b**R*)-6-hydroxy-10,11,12,18,19,23b-hexahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-*c*][2,3,6]benzotriazacyclotetradecine-5,7-dione (compound **86A**, 9 mg) was obtained using the procedure described for compound **28A**.

Compound **86A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.91 (br s, 1H), 7.25 - 7.32 (m, 2H), 7.18 - 7.22 (m, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.05 (dd, *J*=6.9, 1.9 Hz, 1H), 6.96 (d, *J*=7.6 Hz, 1H), 6.91 (t, *J*=7.3 Hz, 1H), 6.69 (d, *J*=7.3 Hz, 1H), 6.39 (d, *J*=11.3 Hz, 1H), 5.88 (br ddd, *J*=11.0, 9.5, 4.4 Hz, 1H), 5.48 (s, 1H), 5.41 (d, *J*=7.6 Hz, 1H), 4.93 (d, *J*=13.2 Hz, 1H), 4.54 (br td, *J*=14.0, 5.2 Hz, 1H), 4.11 (d, *J*=13.2 Hz, 1H), 3.64 (br ddd, *J*=13.6, 8.8, 2.5 Hz, 1H), 3.54 (br d, *J*=18.0 Hz, 1H), 2.94 (br ddd, *J*=18.5, 13.8, 4.9 Hz, 1H), 2.74 - 2.80 (m, 1H), 2.39 - 2.46 (m, 2H), 2.06 - 2.14 (m, 1H), 1.86 - 1.96 (m, 1H), 1.70 - 1.79 (m, 1H), 1.49 - 1.59 (m, 1H), 1.26 - 1.37 (m, 1H).

LC/MS (method LC-C): Rt 3.35 min, MH⁺ 454

$[\alpha]_D^{20}$: +86.54 ° (c 0.104, DMF)

Chiral HPLC (method HPLC-B): Rt 5.74 min, chiral purity 100%

Synthesis of compound **86B**:

(13**Z*,23b**R*)-6-hydroxy-10,11,12,18,19,23b-hexahydro-9*H*-1,8-methanobenzo[4,5]cyclohepta[1,2,3-*qr*]pyrido[1,2-*c*][2,3,6]benzotriazacyclotetradecine-5,7-dione (compound **86B**, 6 mg) was obtained using the procedure described for compound **28A**.

Compound **86B**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.88 (br s, 1H), 7.26 - 7.33 (m, 2H), 7.17 - 7.23 (m, 1H), 7.11 - 7.15 (m, 1H), 7.05 (dd, *J*=6.9, 1.6 Hz, 1H), 6.96 (d, *J*=7.6 Hz, 1H), 6.91

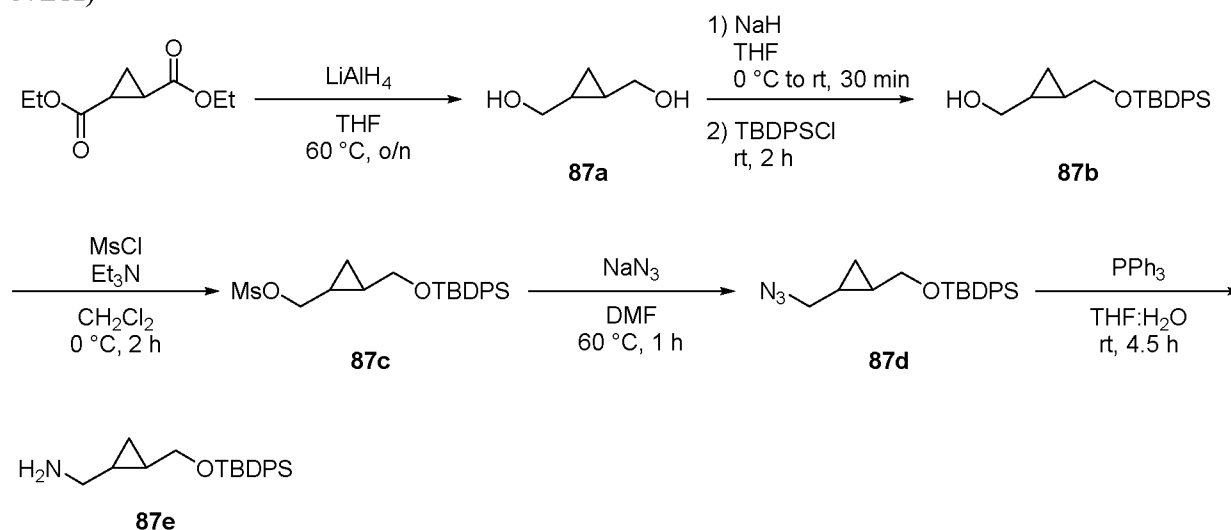
(t, $J=7.4$ Hz, 1H), 6.69 (d, $J=6.9$ Hz, 1H), 6.39 (d, $J=11.3$ Hz, 1H), 5.85 - 5.91 (m, 1H), 5.49 (s, 1H), 5.41 (d, $J=7.6$ Hz, 1H), 4.93 (d, $J=12.9$ Hz, 1H), 4.54 (br td, $J=13.9, 5.0$ Hz, 1H), 4.11 (d, $J=12.9$ Hz, 1H), 3.60 - 3.67 (m, 1H), 3.54 (br d, $J=17.7$ Hz, 1H), 2.94 (br ddd, $J=18.4, 13.8, 4.7$ Hz, 1H), 2.74 - 2.81 (m, 1H), 2.40 - 2.45 (m, 2H), 2.06 - 2.14 (m, 1H), 1.87 - 1.96 (m, 1H), 1.70 - 1.80 (m, 1H), 1.50 - 1.59 (m, 1H), 1.27 - 1.37 (m, 1H).

LC/MS (method LC-C): Rt 3.35 min, MH^+ 454

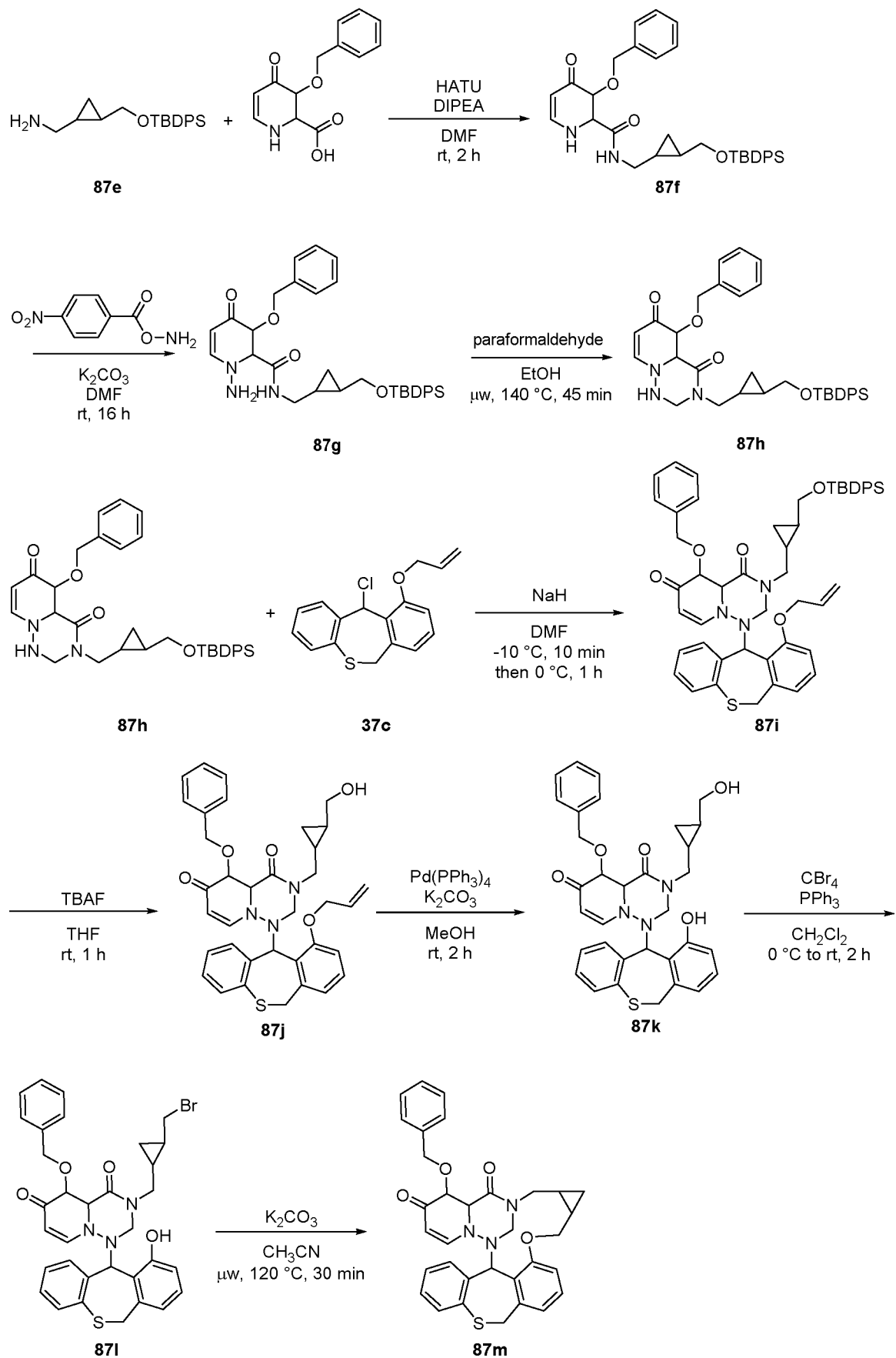
$[\alpha]_D^{20}$: -135.29° (c 0.102, DMF)

Chiral HPLC (method HPLC-B): Rt 7.11 min, chiral purity 100%

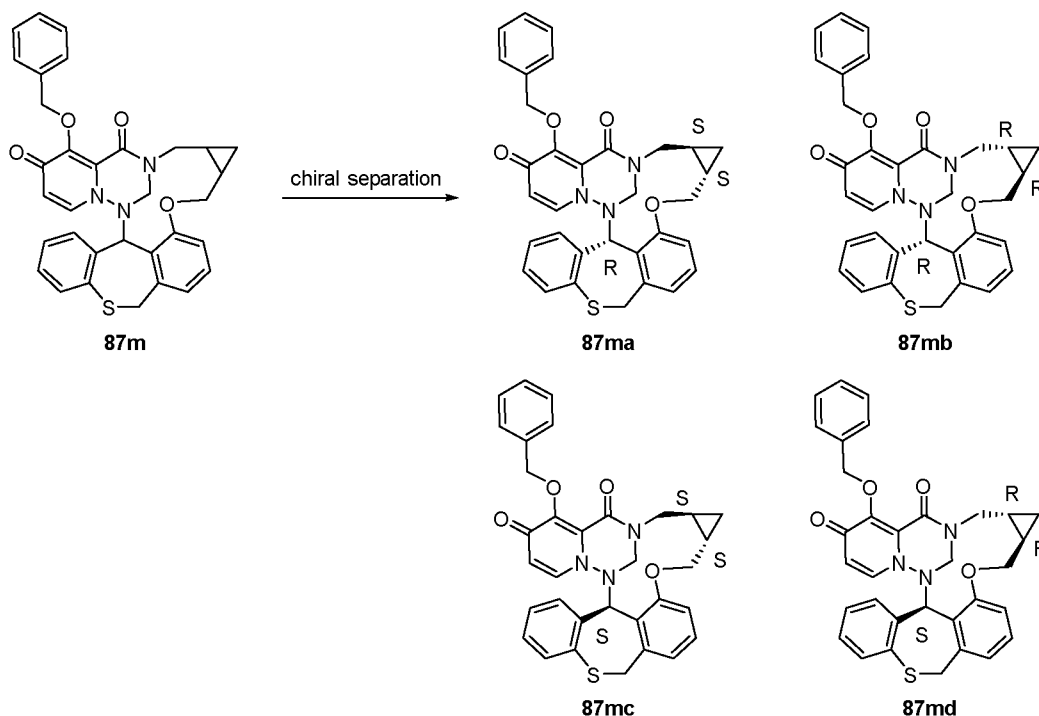
- 10 **Example 87:** synthesis of (1*aS*,11*bR*,20*aS*)-17-hydroxy-1*a*,2,6,11*b*,20,20*a*-hexahydro-1*H*-5,4-(epi*prop*[1]*en*[1]*yl*[3]*ylidene*)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **87AA**), (1*aR*,11*bS*,20*aR*)-17-hydroxy-1*a*,2,6,11*b*,20,20*a*-hexahydro-1*H*-5,4-(epi*prop*[1]*en*[1]*yl*[3]*ylidene*)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **87BB**), (1*aR*,11*bR*,20*aR*)-17-hydroxy-1*a*,2,6,11*b*,20,20*a*-hexahydro-1*H*-5,4-(epi*prop*[1]*en*[1]*yl*[3]*ylidene*)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **87AB**) and (1*aS*,11*bS*,20*aS*)-17-hydroxy-1*a*,2,6,11*b*,20,20*a*-hexahydro-1*H*-5,4-(epi*prop*[1]*en*[1]*yl*[3]*ylidene*)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **87BA**)



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-233-



Synthesis of intermediate **87a**:

To a solution of diethyl *trans*-1,2-cyclopropanedicarboxylate [CAS 3999-55-1] (9.85 g, 52.9 mmol) in anhydrous THF (150 mL) under nitrogen atmosphere at 0 °C was added
 5 LiAlH₄ (1.0 M in THF, 80 mL, 80 mmol) dropwise. The reaction mixture was stirred at 60 °C overnight. The reaction was quenched by the addition of water followed by a 15% aqueous solution of NaOH and water again. The mixture was filtered over a pad of Celite® and washed with EtOAc. The filtrate was partially concentrated in vacuo, dried over Na₂SO₄, filtered and concentrated in vacuo to afford [2 cyclopropane-1,2-diyldimethanol (intermediate **87a**, 4.9 g).

Synthesis of intermediate **87b**:

To a solution of intermediate **87a** (4.90 g, 48.0 mmol) in anhydrous THF (200 mL) at 0 °C under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 2.30 g, 57.6 mmol) portionwise. The mixture was stirred at rt for 30 minutes and TBDPSCl (12.5 mL, 48.8 mmol) was added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with Et₂O and washed with a saturated aqueous solution of NH₄Cl and brine. The aqueous phase was extracted with Et₂O. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out
 15 by flash column chromatography over silica gel (220 g, petroleum ether/EtOAc from 100/0 to 75/25) to afford (2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methanol (intermediate **87b**, 11.95 g).

Synthesis of intermediate 87c:

(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methyl methanesulfonate (intermediate **87c**, 14.7 g) was obtained using the procedure described for intermediate **80c**.

5

Synthesis of intermediate 87d:

To a solution of intermediate **87c** (14.7 g, 35.1 mmol) in anhydrous DMF (70 mL) under nitrogen atmosphere was added NaN₃ (4.56 g, 70.2 mmol). The reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH₄Cl (twice), water and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to afford ((2-(azidomethyl)cyclopropyl)methoxy)(*tert*-butyl)diphenylsilane (intermediate **87d**, 12.8 g).

10

Synthesis of intermediate 87e:

(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methanamine (intermediate **87e**, 9.74 g) was obtained using the procedure described for intermediate **80e**. Crude intermediate **87e** was purified by flash chromatography over silica gel (220 g, CH₂Cl₂/(CH₂Cl₂/MeOH/Et₃N 90/9/1) from 100/0 to 90/10).

15

20

Synthesis of intermediate 87f:

3-(benzyloxy)-N-((2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxamide (intermediate **87f**, 8.87 g) was obtained using the procedure described for intermediate **5b**.

25

Synthesis of intermediate 87g:

To a solution of intermediate **87f** (8.87 g, 15.7 mmol) in anhydrous DMF (80 mL) under nitrogen atmosphere was suspended K₂CO₃ (6.45 g, 46.7 mmol). After 5 min *o*-(4-nitrobenzoyl)hydroxylamine [CAS35657-36-3] (4.28 g, 23.5 mmol) was added. The reaction mixture was stirred at rt for 16 h, then at 35 °C for 24 h. The reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH₄Cl (twice), water and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash column chromatography on silica gel (220 g, CH₂Cl₂/MeOH from 100/0 to 96/4) to afford 1-amino-3-(benzyloxy)-N-((2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxamide (intermediate **87g**, 6.51 g).

30

35

Synthesis of intermediate 87h:

5-(benzyloxy)-3-((2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methyl)-2,3,4a,5-tetrahydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **87h**, 4.48 g) was obtained using the procedure described for intermediate **5d**. Crude intermediate **87h** was purified by flash column chromatography over silica gel (220 g, CH₂Cl₂/MeOH from 100:0 to 94:6).

Synthesis of intermediate 87i:

Intermediate **87h** (2.00 g, 3.37 mmol) was dissolved under nitrogen atmosphere in anhydrous DMF (25 mL). The solution was cooled to -10 °C and NaH (60% dispersion in mineral oil, 162 mg, 4.04 mmol) was added. After stirring for 10 min a solution of intermediate **37c** (1.53 g, 5.05 mmol) in anhydrous DMF (5 mL) was added dropwise. The reaction mixture was stirred between -10 and 0 °C for 1 h. The reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH₄Cl (4 times). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash column chromatography over silica gel (120 g, CH₂Cl₂/MeOH from 100/0 to 97/3) to afford 1-(10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-5-(benzyloxy)-3-((2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methyl)-2,3,4a,5-tetrahydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **87i**, 2.5 g).

Synthesis of intermediate 87j:

To a solution of intermediate **87i** (2.50 g, 2.91 mmol) in anhydrous THF (30 mL) under nitrogen atmosphere was added TBAF (1.0 M in THF, 3.2 mL, 3.20 mmol) dropwise. The reaction mixture was stirred at rt for 1 h and concentrated in vacuo. Purification was carried out by flash column chromatography over silica gel (120 g, CH₂Cl₂/MeOH from 100/0 to 96/4) to afford 1-(10-(allyloxy)-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-5-(benzyloxy)-3-((2-(hydroxymethyl)cyclopropyl)methyl)-2,3,4a,5-tetrahydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **87j**, 1.5 g).

Synthesis of intermediate 87k:

Intermediate **87j** (1.50 g, 2.41 mmol) was dissolved in MeOH (50 mL) under nitrogen atmosphere. Pd(PPh₃)₄ (279 mg, 241 μmol) was added and the mixture was stirred for 10 min. K₂CO₃ (1.00 g, 7.24 mmol) was added and the reaction mixture was stirred at rt for 2 h. The mixture was filtered over a pad of Celite®. The filtrate was diluted with CH₂Cl₂ and washed with water and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification was carried out by flash column chromatography over silica gel (80 g, CH₂Cl₂ /MeOH/aq.NH₃ from 100/0 to 90/10) to afford 5-(benzyloxy)-1-(10-

hydroxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-3-((2-(hydroxymethyl)cyclopropyl)methyl)-2,3,4 α ,5-tetrahydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **87k**, 1.3 g).

5 **Synthesis of intermediate 87l:**

Intermediate **87k** (900 mg, 1.55 mmol) was dissolved in anhydrous CH₂Cl₂ (30 mL) under nitrogen atmosphere. The solution was cooled to 0 °C and PPh₃ (675 mg, 3.09 mmol) was added. After stirring for 15 min, CBr₄ (1.03 g, 3.09 mmol) was added. The reaction mixture was stirred at rt for 2 h and concentrated in vacuo. Purification was carried out by flash column chromatography over silica gel (40 g, CH₂Cl₂/MeOH from 100/0 to 98/2) to afford 5-(benzyloxy)-3-((2-(bromomethyl)cyclopropyl)methyl)-1-(10-hydroxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-2,3,4 α ,5-tetrahydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **87l**, 850 mg).

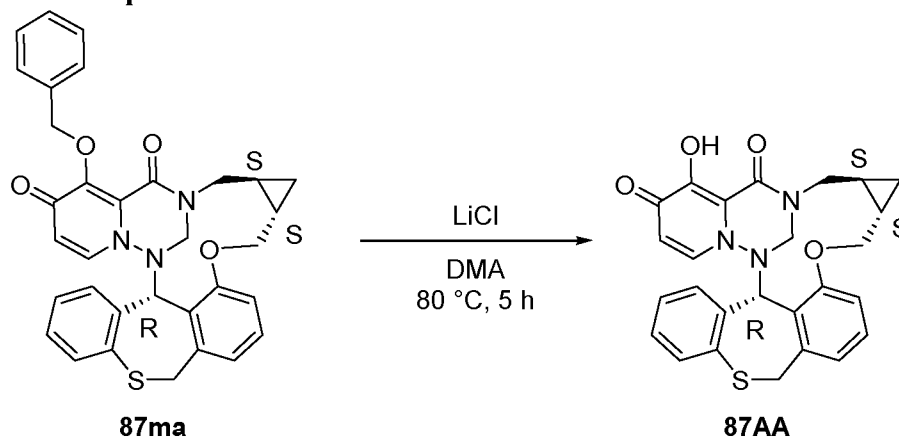
15 **Synthesis of intermediate 87m:**

17-(benzyloxy)-1a,2,6,11b,17,17a,20,20a-octahydro-1*H*-5,4-(epi-prop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropana[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (intermediate **87m**) was obtained using the procedure described for intermediate **80m**. Crude intermediate **87m** was purified by flash column chromatography over silica gel (40 g, CH₂Cl₂/MeOH from 100/0 to 97/3). A second purification was performed by flash column chromatography C18 (40 μ m, 45 g, H₂O/MeOH from 70/30 to 0/100) to afford intermediate **87m** (508 mg) as a mixture of diastereoisomers.

The isomers were separated via chiral SFC (Stationary phase: CHIRALPAK AS-H 5 μ m 250*20mm, Mobile phase: 60% CO₂, 40% MeOH) to afford two fractions: fraction A (intermediates **87ma** and **87mb**, 192 mg) and fraction B (intermediates **87mc** and **87md**, 195 mg).

The diastereoisomers **87ma** and **87mb** were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 μ m 250*30mm, Mobile phase: 55% CO₂, 45% EtOH) to afford intermediate **87ma** (85 mg) and intermediate **87mb** (72 mg).

The diastereoisomers **87mc** and **87md** were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5 μ m 250*21.2mm, Mobile phase: 50% CO₂, 50% (EtOH+10% CH₂Cl₂) to afford intermediate **87md** (79 mg) and intermediate **87mc** (75 mg).

Synthesis of compound 87AA:

(1a*S*,11b*R*,20a*S*)-17-hydroxy-1a,2,6,11*b*,20,20a-hexahydro-1*H*-5,4-(epi)prop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-
 5 *c*]cyclopropano[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (compound **87AA**, 44 mg) was obtained using the procedure described for compound **28A**.

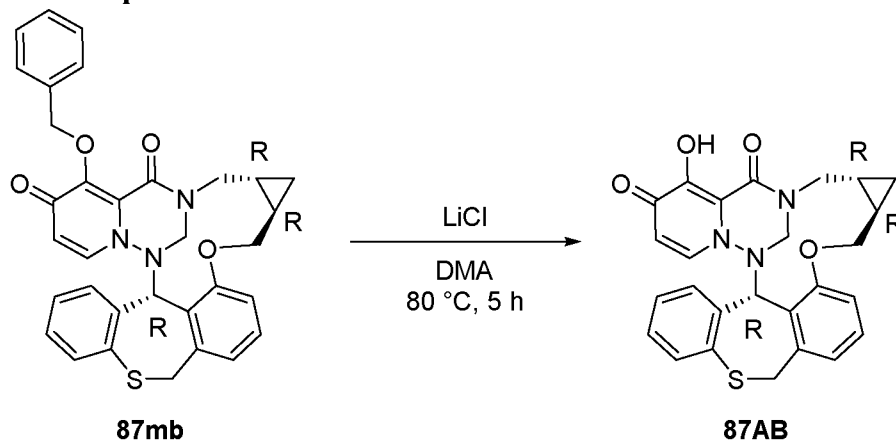
Compound 87AA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.34 (t, *J*=7.9 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H),
 10 7.03 - 7.15 (m, 4H), 6.85 (td, *J*=7.6, 1.2 Hz, 1H), 6.73 - 6.79 (m, 1H), 6.09 (s, 1H), 5.75
 (d, *J*=13.6 Hz, 1H), 5.61 (d, *J*=7.9 Hz, 1H), 5.06 (d, *J*=13.2 Hz, 1H), 4.83 (dd, *J*=12.6,
 4.7 Hz, 1H), 4.49 (d, *J*=13.6 Hz, 1H), 3.86 (d, *J*=13.2 Hz, 1H), 3.51 (dd, *J*=14.0, 10.9
 Hz, 2H), 3.17 (dd, *J*=14.5, 5.0 Hz, 1H), 1.31 - 1.39 (m, 1H), 0.80 - 0.88 (m, 1H), 0.74 -
 0.79 (m, 1H), 0.65 (dt, *J*=8.4, 5.0 Hz, 1H).

15 LC/MS (method LC-C): Rt 2.72 min, MH⁺ 474

[α]_D²⁰: +170.77 ° (c 0.284, DMF)

Chiral HPLC (method HPLC-B): Rt 6.89 min, chiral purity 100%

Synthesis of compound 87AB:

(1a*R*,11b*R*,20a*R*)-17-hydroxy-1*a*,2,6,11b,20,20a-hexahydro-1*H*-5,4-(epiprop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (compound **87AB**, 28 mg) was obtained using the procedure described for compound **28A**.

5

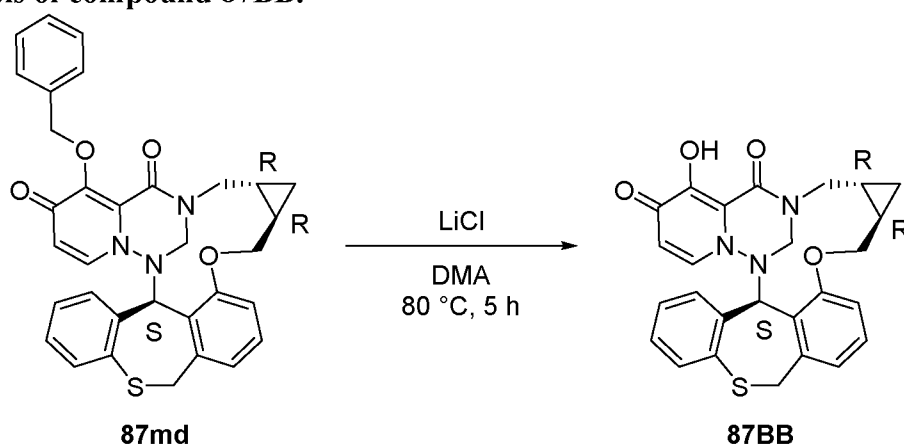
Compound 87AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.58 (br s, 1 H), 7.45 (d, *J*=7.9 Hz, 1H), 7.35 - 7.43 (m, 2H), 7.07 - 7.15 (m, 2H), 7.02 - 7.05 (m, 1H), 6.85 (br td, *J*=7.4, 1.3 Hz, 1H), 6.76 (dd, *J*=7.7, 1.1 Hz, 1H), 6.18 (s, 1H), 5.93 (d, *J*=13.6 Hz, 1H), 5.61 (d, *J*=7.6 Hz, 1H), 5.11 (d, *J*=13.2 Hz, 1H), 4.91 (dd, *J*=12.3, 3.5 Hz, 1H), 4.38 (d, *J*=13.2 Hz, 1H), 4.30 (dd, *J*=13.6, 2.5 Hz, 1H), 3.85 (d, *J*=13.6 Hz, 1H), 3.29 - 3.37 (m, 1H), 2.17 (dd, *J*=13.7, 11.2 Hz, 1H), 1.24 - 1.32 (m, 1H), 1.08 - 1.15 (m, 1H), 0.61 (dt, *J*=8.9, 4.7 Hz, 1H), 0.42 (dt, *J*=8.8, 5.2 Hz, 1H).

LC/MS (method LC-C): Rt 2.69 min, MH⁺ 474

15 $[\alpha]_D^{20}$: +283.46 ° (c 0.254, DMF)

Chiral HPLC (method HPLC-B): Rt 6.85 min, chiral purity 100%

Synthesis of compound 87BB:

20 (1a*R*,11b*S*,20a*R*)-17-hydroxy-1*a*,2,6,11b,20,20a-hexahydro-1*H*-5,4-(epiprop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-*c*]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (compound **87BB**, 32 mg) was obtained using the procedure described for compound **28A**.

Compound 87BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.27 (t, *J*=7.9 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 6.95 - 7.09 (m, 4H), 6.74 - 6.84 (m, 1H), 6.69 (d, *J*=7.6 Hz, 1H), 6.02 (s, 1H), 5.68 (d, *J*=13.6 Hz, 1H), 5.54 (d, *J*=7.6 Hz, 1H), 4.99 (d, *J*=13.2 Hz, 1H), 4.76 (dd, *J*=12.6, 4.7 Hz, 1H), 4.42 (d, *J*=13.6 Hz, 1H), 3.79 (d, *J*=13.2 Hz, 1H), 3.40 - 3.48 (m, 2H), 3.10 (br

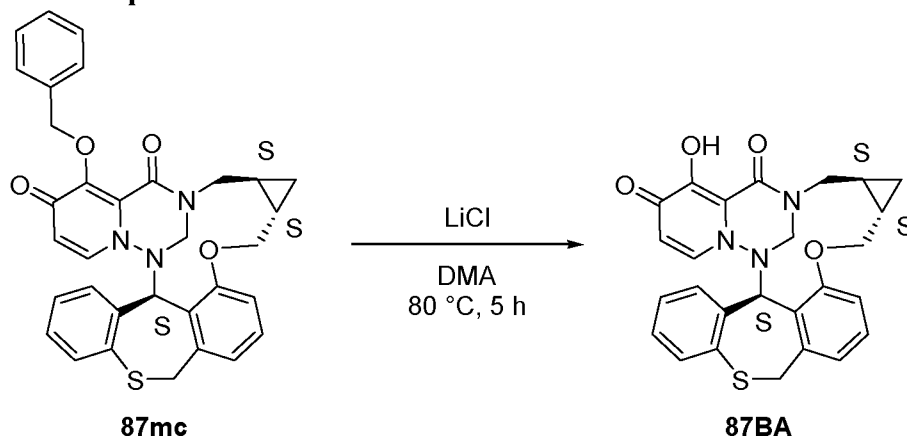
dd, $J=14.3, 5.2$ Hz, 1H), 1.24 - 1.33 (m, 1H), 0.73 - 0.81 (m, 1H), 0.70 (dt, $J=8.4, 4.5$ Hz, 1H), 0.58 (dt, $J=8.2, 4.7$ Hz, 1H).

LC/MS (method LC-C): Rt 2.72 min, MH^+ 474

$[\alpha]_D^{20}$: -162.80 ° (c 0.250, DMF)

5 Chiral HPLC (method HPLC-B): Rt 9.48 min, chiral purity 100%

Synthesis of compound 87BA:



(1a*S*,11b*S*,20a*S*)-17-hydroxy-1a,2,6,11b,20,20a-hexahydro-1*H*-5,4-

10 (epiprop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiipino[4,5-
c]cyclopropa[*k*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (compound
87BA, 23 mg) was obtained using the procedure described for compound **28A**.

Compound 87BA:

15 ^1H NMR (500 MHz, DMSO- d_6) δ ppm 11.53 (br s, 1H), 7.45 (d, $J=7.9$ Hz, 1H), 7.35 -
7.43 (m, 2H), 7.08 - 7.17 (m, 2H), 7.01 - 7.07 (m, 1H), 6.85 (t, $J=7.4$ Hz, 1H), 6.76 (d,
 $J=7.3$ Hz, 1H), 6.18 (s, 1H), 5.93 (d, $J=13.2$ Hz, 1H), 5.61 (d, $J=7.6$ Hz, 1H), 5.11 (d,
20 $J=13.6$ Hz, 1H), 4.91 (dd, $J=12.0, 3.2$ Hz, 1H), 4.38 (d, $J=13.6$ Hz, 1H), 4.30 (dd, $J=13.6,$
2.2 Hz, 1H), 3.85 (d, $J=13.6$ Hz, 1H), 3.36 (br s, 1H), 2.17 (dd, $J=13.6, 11.3$ Hz, 1H),
1.24 - 1.33 (m, 1H), 1.07 - 1.16 (m, 1H), 0.61 (dt, $J=9.1, 4.8$ Hz, 1H), 0.42 (dt, $J=9.2, 4.7$
Hz, 1H).

LC/MS (method LC-C): Rt 2.69 min, MH^+ 474

$[\alpha]_D^{20}$: -315.35 ° (c 0.241, DMF)

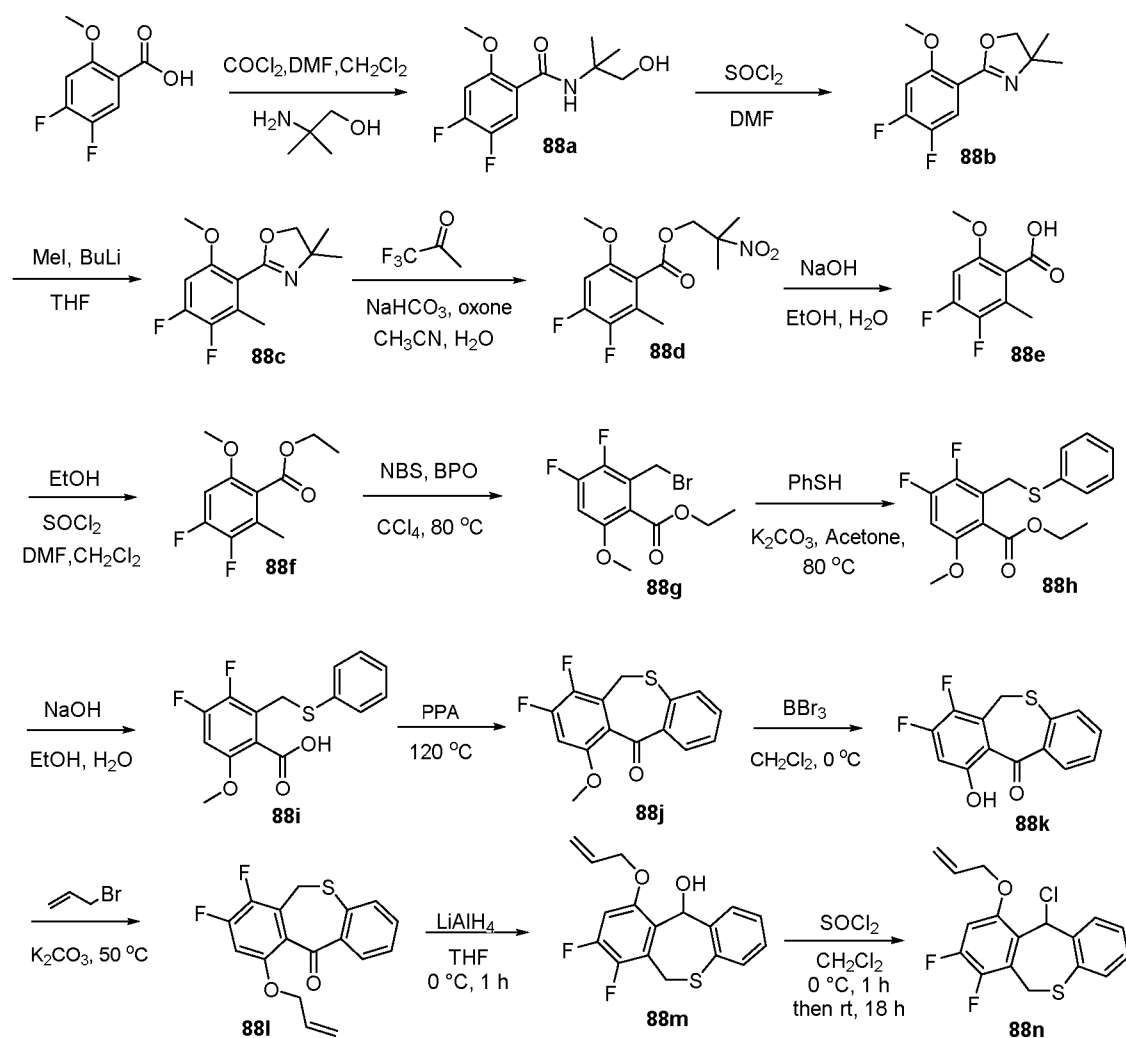
Chiral HPLC (method HPLC-B): Rt 10.12 min, chiral purity 100%

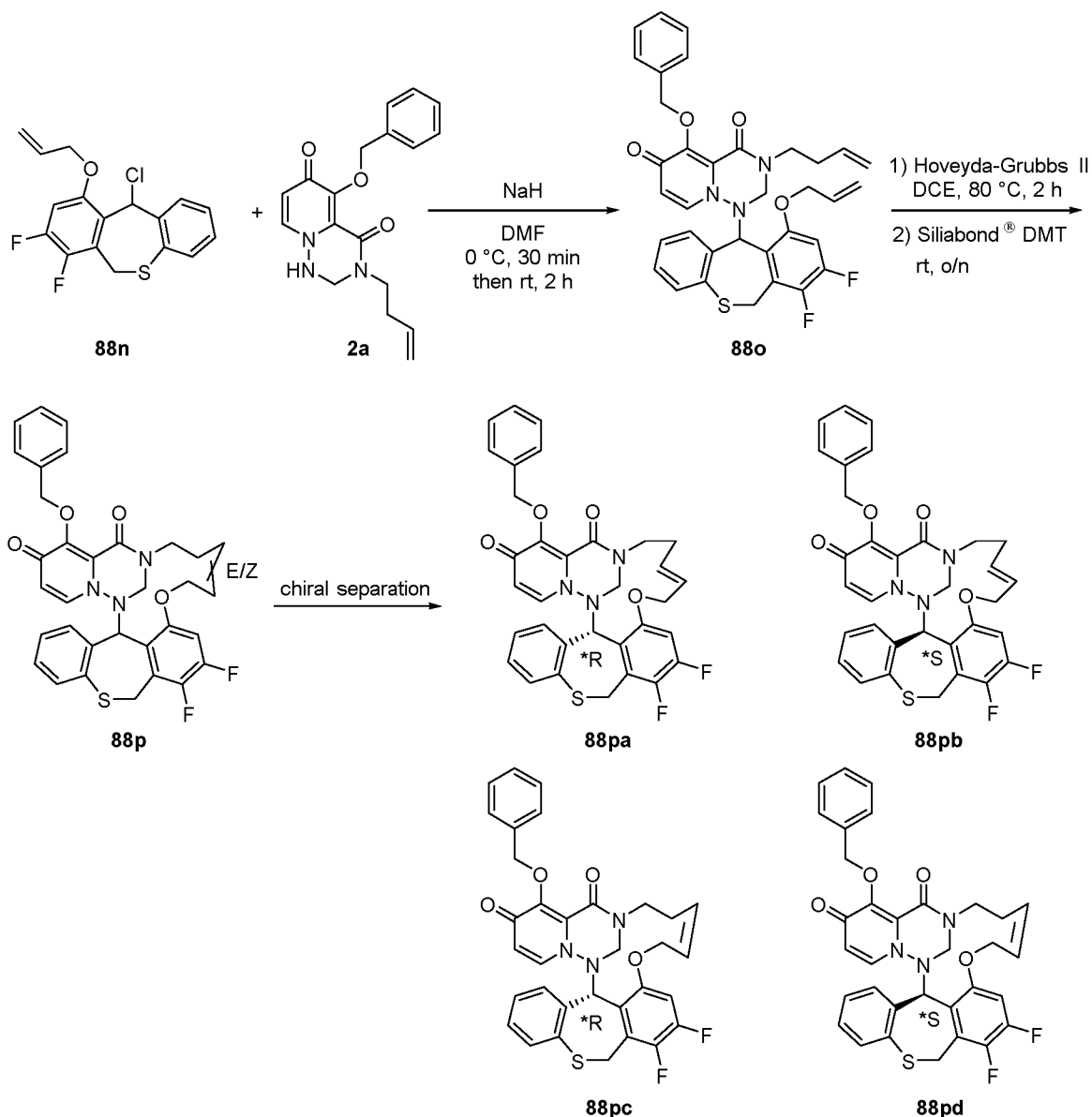
25

Example 88: synthesis of (23b**R*, *Z*)-16,17-difluoro-6-hydroxy-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiipino[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione

(Compound **88A**), (23b**S*, *Z*)-16,17-difluoro-6-hydroxy-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (Compound **88B**), (23b**R*, *E*)-16,17-difluoro-6-hydroxy-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (Compound **88C**) and (23b**S*, *E*)-16,17-difluoro-6-hydroxy-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (Compound **88D**)

10





Synthesis of intermediate 88a:

To a solution of 4,5-difluoro-2-methoxybenzoic acid [CAS 425702-18-7] (32.05 g, 170.37 mmol) in CH_2Cl_2 (300 mL) was added DMF (660 μL , 8.52 mmol) and oxalyl chloride (17.6 mL, 204.44 mmol) dropwise at 0°C. The light yellow mixture was stirred at rt for 2h. Then the mixture was concentrated in vacuo. The solution of the residue in CH_2Cl_2 (150 mL) was added dropwise into a solution of 2-amino-2-methylpropan-1-ol (27.6 mL, 289.6 mmol) in CH_2Cl_2 (200 mL) at 0°C. The mixture was stirred at rt for 12h.

The solids were filtered and the filtrate was washed with water (300 mL), 5% NaHCO_3 in H_2O (300 mL) and 1M HCl (300 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo to afford 42.7 g of 4,5-difluoro-*N*-(1-hydroxy-2-methylpropan-2-yl)-2-methoxybenzamide (intermediate **88a**) as a white solid, which was used as such in the next step.

Synthesis of intermediate 88b:

To a solution of intermediate **88a** (42.7 g, 164.71 mmol) in CH₂Cl₂ (500 mL) was added DMF (640 µL, 8.24 mmol) and thionyl chloride (35.8 mL, 494.12 mmol) dropwise at 0°C. The yellow mixture was stirred at rt for 3h. The reaction was concentrated in vacuo and quenched with water (500 mL). pH was adjusted to 8 with 5N aq solution of NaOH and the solution was extracted with CH₂Cl₂ (3x500 mL). The combined organic layer were washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (330 g, eluent petroleum ether/EtOAc (100:0 to 30:70)) to give 2-(4,5-difluoro-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (intermediate **88b**, 21 g) as a white solid.

Synthesis of intermediate 88c:

To a solution of intermediate **88b** (10.0 g, 41.5 mmol) in THF (300 mL) was added *n*-BuLi (19.9 mL, 49.7 mmol) at -78°C over 15 min under N₂. The yellow mixture was stirred at -78°C for 30 min, then MeI (7.8 mL, 125.1 mmol) was added dropwise at -78°C over 15 min. The mixture was stirred at -78°C for 30 min and then warmed-up to rt for 30 min. The reaction mixture was quenched by addition of a saturated solution of NH₄Cl in water (300 mL), and extracted with EtOAc twice. The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Grace 120 g, eluent petroleum ether/EtOAc (100:0 to 60:40) to give 4.4 g of 2-(3,4-difluoro-6-methoxy-2-methylphenyl)-4,4-dimethyl-4,5-dihydrooxazole (intermediate **88c**).

Synthesis of intermediate 88d:

To a solution of intermediate **88c** (14.0 g, 54.85 mmol) in CH₃CN (300 mL) was added 1,1,1-trifluoropropan-2-one (49.2 g, 438.8 mmol) at rt. Then a mixture of NaHCO₃ (110.6 g, 1.316 mol) and oxone (134.9 g, 439 mmol) in water (60 mL) was added over 10 min at 0°C. The yellow mixture was stirred at rt for 16h. The reaction mixture was filtered and washed with CH₂Cl₂ and the organic layer was concentrated in vacuo. The residue was purified by flash chromatography (Grace 220 g, eluent petroleum ether/EtOAc (100:0 to 80:20)) to give 2-methyl-2-nitropropyl 3,4-difluoro-6-methoxy-2-methylbenzoate (intermediate **88d**, 13 g).

Synthesis of intermediate 88e:

To a solution of intermediate **88d** (13 g, 42.9 mmol) in EtOH (80 mL) was added water (80 mL) and NaOH (8.6 g, 214.3 mmol) at 0°C. The yellow mixture was stirred at 60°C for 2h. The reaction mixture was concentrated in vacuo. Water was added to the residue (200 mL) and the solution was extracted with methyl tert-butyl ether (2x100 mL). The

aqueous layer was acidified with 6N HCl, extracted with CH₂Cl₂ (3x20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford 3,4-difluoro-6-methoxy-2-methylbenzoic acid (intermediate **88e**, 8.2 g).

5 **Synthesis of intermediate 88f:**

To a solution of intermediate **88e** (7.5 g, 37.10 mmol) in CH₂Cl₂ (100 mL) was added DMF (144 µL, 1.86 mmol) and SOCl₂ (3.2 mL, 44.52 mmol) dropwise at 0°C. The yellow mixture was stirred at rt for 2h. The reaction mixture was concentrated in vacuo. EtOH (30 mL) was added to the residue at 0°C and the reaction was stirred for 30 min at rt. The reaction mixture was concentrated and the residue was purified by flash chromatography (Grace 120 g, eluent petroleum ether/EtOAc (100:0 to 90:10) to give ethyl 3,4-difluoro-6-methoxy-2-methylbenzoate (intermediate **88f**, 6.9 g) as a colorless oil.

15 **Synthesis of intermediate 88g:**

Benzoyl peroxide (3.16 g, 13.03 mmol) was added to a stirred solution of intermediate **88f** (60.0 g, 260.63 mmol) and NBS (51.0 g, 286.70 mmol) in CCl₄ (1440 mL) at 25°C. Then the mixture was heated to 80°C and stirred at reflux for 4 h. A brownish solution was formed. The mixture was poured into water (1000 mL) and extracted with CH₂Cl₂ (800 mL x 3). The combined organic layer was washed with brine (1000 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford ethyl 2-(bromomethyl)-3,4-difluoro-6-methoxybenzoate (intermediate **88g**, 60.0 g, crude) as a yellow oil. The compound was used as such in the next step.

25 **Synthesis of intermediate 88h:**

Intermediate **88g** (60.0 g, 194.11 mmol) was dissolved in acetone (840 mL). K₂CO₃ (40.24 g, 291.16 mmol) and benzenethiol (32.5 g, 294.98 mmol, 30.09 mL, 1.52 eq) was added and the mixture was stirred at 80°C for 4 hours. A brownish mixture was formed. The mixture was filtered and concentrated in vacuum to give a brown solid. Crude product was triturated with MTBE (150 mL) and filtered. The residue was dried in vacuum to give ethyl 3,4-difluoro-6-methoxy-2-((phenylthio)methyl)benzoate (intermediate **88h**, 60.0 g, 163.14 mmol) as a brown solid.

Synthesis of intermediate 88i:

35 To a solution of intermediate **88h** (55.0 g, 162.54 mmol) in EtOH (1050 mL) was added NaOH (2 M, 406.36 mL) at 25°C. The solution was heated at 80°C and stirred at reflux for 4 hours. A brown solution was formed. The solution was concentrated in vacuum, then water (300 mL) was added and the mixture was made acidic (pH=2) with

diluted 2N hydrochloric acid and extracted with ethyl acetate (300 mL x 3). The combined organic phase was washed with brine (300 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford 3,4-difluoro-6-methoxy-2-((phenylthio)methyl)benzoic acid (intermediate **88i**, 50.0 g, crude) as a brown oil.

5

Synthesis of intermediate 88j:

Intermediate **88i** (10.0 g, 32.23 mmol, 1 eq) was added in polyphosphoric acid (150.0 g, 443.88 mmol, 13.77 eq) at 25°C. The mixture was stirred for 4 hours at 120°C. A dark red solution was formed. The residue was poured into ice-water (500 mL) and stirred. The aqueous phase was extracted with ethyl acetate (500 mLx3). The combined organic phase was washed with brine (500 mLx3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with MTBE (150 mL) and filtered. The residue was dried in vacuum to afford 7,8-difluoro-10-methoxydibenzo[*b,e*]thiepin-11(6*H*)-one (intermediate **88j**, 30.0 g) as a brown solid.

15

Synthesis of intermediate 88k:

To a mixture of intermediate **88j** (13.1 g, 44.82 mmol, 1 eq) in CH₂Cl₂ (180 mL), a solution of BBr₃ (1 M, 95.27 mL, 2.13 eq) in CH₂Cl₂ (100 mL) was added dropwise at 0°C. The mixture was stirred at 25°C for 2 hours. A brown solution was formed. An aqueous saturated sodium chloride solution was added, and the mixture was extracted with CH₂Cl₂ (200 mL x 3). Organic layer was washed with brine (200 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford 7,8-difluoro-10-hydroxydibenzo[*b,e*]thiepin-11(6*H*)-one (intermediate **88k**, 11.4 g) as a brown solid.

20

Synthesis of intermediate 88l:

10-(allyloxy)-7,8-difluorodibenzo[*b,e*]thiepin-11(6*H*)-one (intermediate **88l**, 11.8 g) was obtained using the procedure described for intermediate **37a**.

25

Synthesis of intermediate 88m:

10-(allyloxy)-7,8-difluoro-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (intermediate **88m**, 11.2 g) was obtained using the procedure described for intermediate **37b**. Crude intermediate **88m** was purified by flash chromatography over silica gel (Petroleum ether/Ethyl acetate 20/1 to 5:1).

30

Synthesis of intermediate 88n:

10-(allyloxy)-11-chloro-7,8-difluoro-6,11-dihydrodibenzo[*b,e*]thiepine (intermediate **88n**, 680 mg) was obtained using the procedure described for intermediate **37c**.

35

Synthesis of intermediate 88o:

1-(10-(allyloxy)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl)-5-(benzyloxy)-3-(but-3-en-1-yl)-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **88o**, 304 mg) was obtained using the procedure described for intermediate **37d**.

5

Synthesis of intermediate 88p:

(*Z/E*)-6-(benzyloxy)-16,17-difluoro-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione

10 (intermediate **88p**, mixture of *Z* and *E* isomers, 144 mg) was obtained using the procedure described for intermediates **37e** and **37f**.

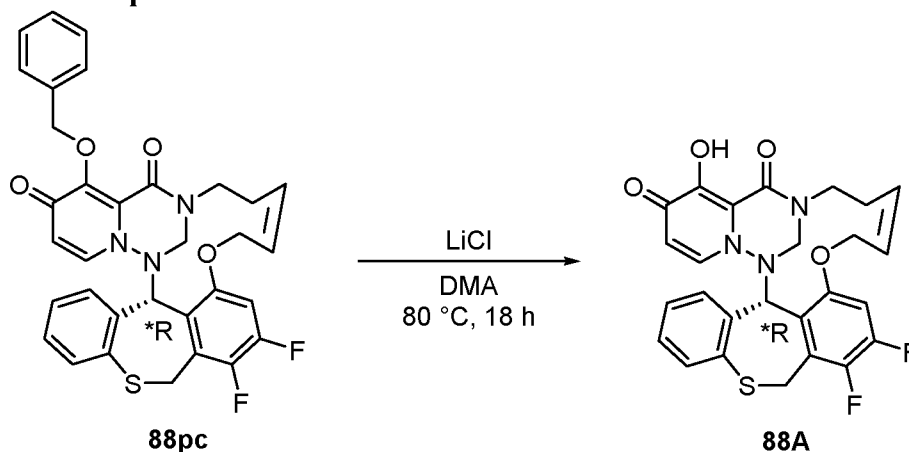
The isomers were separated via reverse phase (Stationary phase: YMC-actus Triart C18 10µm 30*300mm, mobile phase gradient: 0.2% aq.NH₄HCO₃/MeCN from 50/50 to 30/70) to afford a fraction containing the *E* isomers (intermediates **88pa** and **88pb**, 33 mg) and a second fractions of *Z* isomers (intermediates **88pc** and **88pd**, 89 mg).

15

The enantiomers **88pa** and **88pb** were separated via chiral SFC (Stationary phase: Whelk-O1 (S,S) 5µm 250*21.2mm, Mobile phase: 50% CO₂, 50% MeOH) to give the first eluted enantiomer **88pa** (24 mg) and the second eluted enantiomer **88pb** (29 mg).

The enantiomers **88pc** and **88pd** were separated via chiral SFC (Stationary phase: CHIRALPAK AS-H 5µm 250*20mm, Mobile phase: 45% CO₂, 55% MeOH) to give the first eluted enantiomer **88pc** (62 mg) and the second eluted enantiomer **88pd** (63 mg).

20

Synthesis of compound 88A:

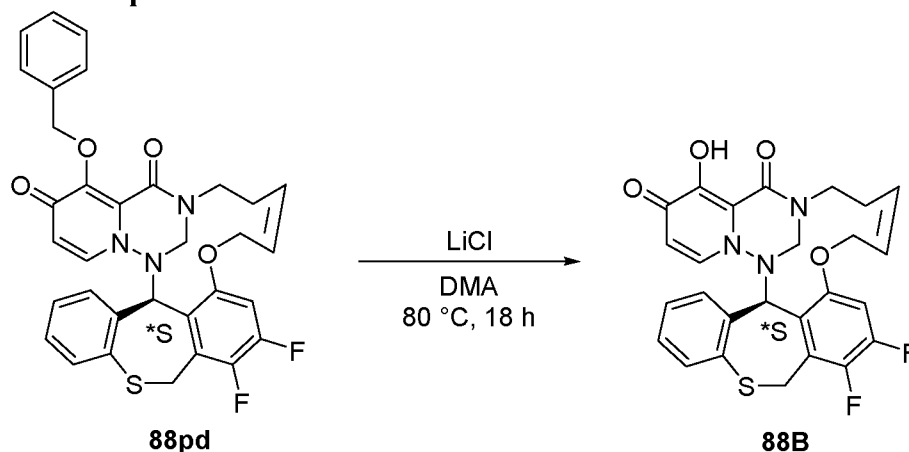
Compound 88A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.70 (br s, 1H), 7.23 (br dd, *J*=12.1, 6.8 Hz, 1H), 7.14 (d, *J*=7.6 Hz, 1H), 6.99 - 7.10 (m, 2H), 6.77 (t, *J*=7.3 Hz, 1H), 6.51 (d, *J*=7.6 Hz, 1H), 5.96 - 6.03 (m, 1H), 5.88 - 5.95 (m, 2H), 5.54 (dd, *J*=14.3, 1.4 Hz, 1H), 5.49 (d, *J*=7.9 Hz, 1H), 4.86 (br d, *J*=13.6 Hz, 1H), 4.41 - 4.49 (m, 2H), 4.37 (d, *J*=13.2 Hz, 1H), 4.18 (br t, *J*=12.5 Hz, 1H), 4.00 (d, *J*=14.2 Hz, 1H), 2.74 (br d, *J*=14.2 Hz, 1H), 2.20 - 2.27 (m, 1H), 2.11 (br d, *J*=14.8 Hz, 1H).

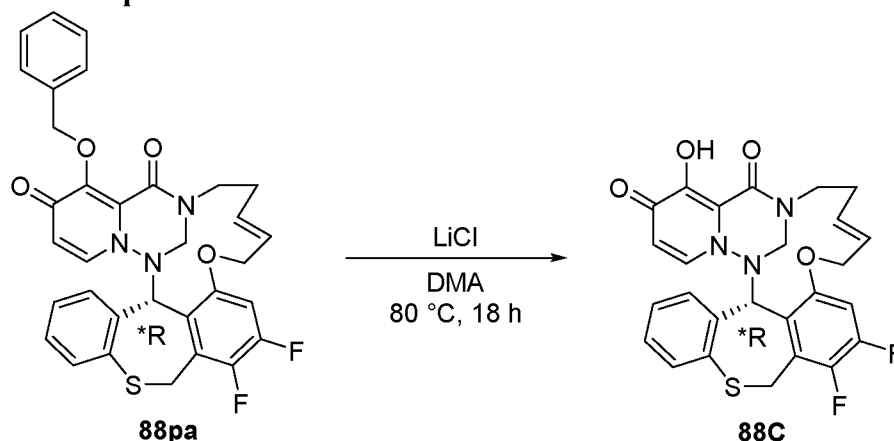
LC/MS (method LC-C): Rt 2.96 min, MH⁺ 510

[α]_D²⁰: +180.18 ° (c 0.111, DMF)

Chiral HPLC (method HPLC-B): Rt 5.72 min, chiral purity 100%

Synthesis of compound 88B:

Synthesis of compound 88C:



(23b**R*, *E*)-16,17-difluoro-6-hydroxy-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (compound **88C**, 9 mg) was obtained using the procedure described for compound **37A**.

Compound 88C:

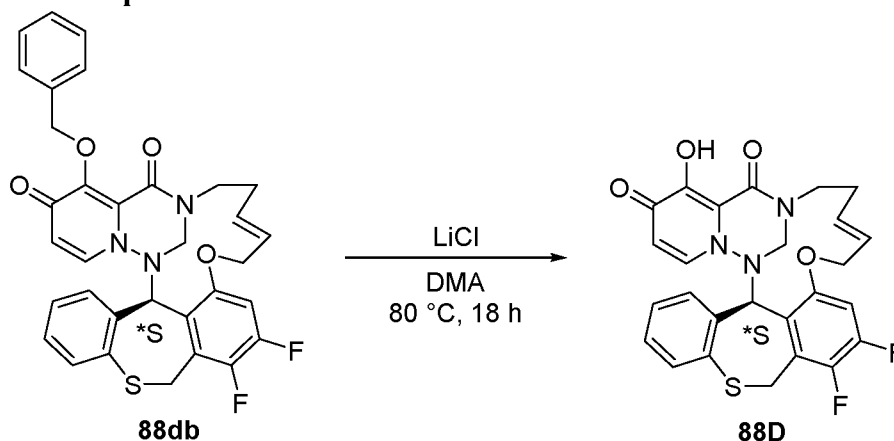
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.92 (br s, 1H), 7.48 (dd, *J*=12.0, 7.3 Hz, 1H), 7.17 (d, *J*=7.6 Hz, 1H), 7.12 - 7.15 (m, 1H), 7.06 - 7.09 (m, 1H), 6.86 - 6.91 (m, 1H), 6.82 - 6.85 (m, 1H), 5.91 (br ddd, *J*=15.1, 9.6, 5.5 Hz, 1H), 5.79 (s, 1H), 5.58 - 5.65 (m, 1H), 5.50 - 5.56 (m, 2H), 4.98 (d, *J*=13.2 Hz, 1H), 4.72 (dd, *J*=11.8, 5.5 Hz, 1H), 4.48 (dd, *J*=11.5, 9.9 Hz, 1H), 4.28 (d, *J*=13.2 Hz, 1H), 4.10 (d, *J*=13.9 Hz, 1H), 3.80 (br dd, *J*=8.8, 3.8 Hz, 1H), 2.78 - 2.85 (m, 2H), 2.18 - 2.25 (m, 1H).

LC/MS (method LC-C): Rt 2.94 min, MH⁺ 510

[α]_D²⁰: +295.05 ° (c 0.101, DMF)

Chiral HPLC (method HPLC-B): Rt 5.78 min, chiral purity 100%

Synthesis of compound 88D:



(23b**S*, *E*)-16,17-difluoro-6-hydroxy-10,13,18,23b-tetrahydro-9*H*-1,8-methano[1]benzothiepine[5,4,3-*lm*]pyrido[2,1-*i*][1,7,10,11]benzoxatriazacyclotetradecine-5,7-dione (compound **88D**, 9 mg) was obtained using the procedure described for compound **37A**.

5

Compound 88D:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.92 (br s, 1H), 7.48 (dd, *J*=12.1, 7.1 Hz, 1H), 7.12 - 7.19 (m, 2H), 7.05 - 7.10 (m, 1H), 6.86 - 6.91 (m, 1H), 6.82 - 6.86 (m, 1H), 5.91 (br ddd, *J*=15.3, 9.6, 5.7 Hz, 1H), 5.79 (s, 1H), 5.58 - 5.66 (m, 1H), 5.50 - 5.56 (m, 2H), 4.97 (d, *J*=12.9 Hz, 1H), 4.72 (dd, *J*=11.8, 5.5 Hz, 1H), 4.48 (dd, *J*=11.7, 10.1 Hz, 1H), 4.28 (d, *J*=13.2 Hz, 1H), 4.10 (d, *J*=13.9 Hz, 1H), 3.80 (br dd, *J*=9.0, 3.9 Hz, 1H), 2.75 - 2.86 (m, 2H), 2.18 - 2.26 (m, 1H).

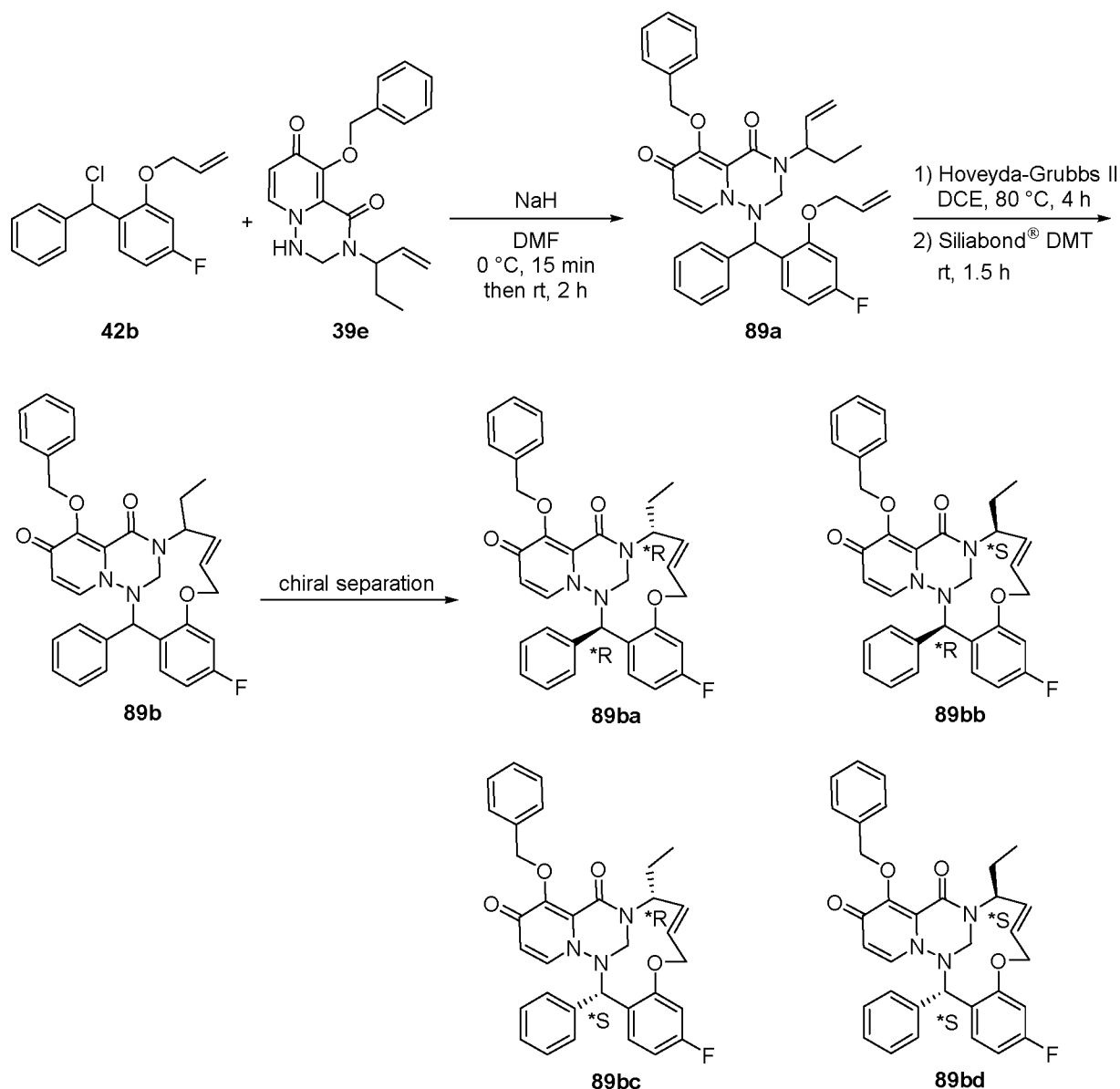
LC/MS (method LC-C): Rt 2.94 min, MH⁺ 510

[α]_D²⁰: -285.45 ° (c 0.110, DMF)

15 Chiral HPLC (method HPLC-B): Rt 8.21 min, chiral purity 100%

Example 89: synthesis of (9**S*,18**R*,*E*)-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **89AA**), (9**R*,18**S*,*E*)-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **89BB**)

20



Synthesis of intermediate **89a**

1-((2-(allyloxy)-4-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-3-(pent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **89a**, 1.08 mg) was obtained using the procedure described for intermediate **85a**. Purification was carried out by flash chromatography over silica gel (80 g, CH₂Cl₂/MeOH from 100/0 to 95/5). A second purification was performed by flash chromatography over silica gel (40 g, petroleum ether/EtOAc from 100/0 to 0/100).

Synthesis of intermediate **89b**

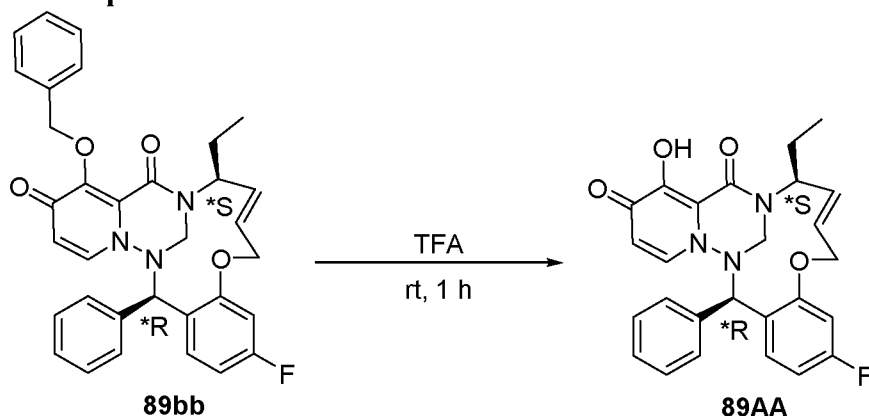
(*E*)-12-(benzyloxy)-9-ethyl-3-fluoro-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(intermediate **89b**, 380 mg) was obtained using the procedure described for intermediate **1f**.

The residue was purified via achiral SFC (Stationary phase: AMINO 5 μ m 150*30 mm, Mobile phase: 85% CO₂, 15% MeOH) to afford two fractions of intermediate **89b** (fraction a: intermediates **89bb** and **89bc**, 247 mg; fraction b: intermediates **89ba** and **89bd**, 111 mg).

The enantiomers **89bb** and **89bc** were separated via chiral SFC (Stationary phase: CHIRALPAK IC 5 μ m 250*30mm, Mobile phase: 50% CO₂, 50% MeOH) to afford **89bb** (90 mg) and **89bc** (95 mg). The enantiomers **89ba** and **89bd** were separated via chiral SFC (Stationary phase: Chiralpak IC 5 μ m 250*21.2mm, Mobile phase: 50% CO₂, 50% MeOH) to afford **89ba** (22 mg) and **89bd** (34 mg).

Synthesis of compound **89AA**:



(9**S*,18**R*,*E*)-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **89AA**, 42 mg) was obtained using the procedure described for compound **1**.

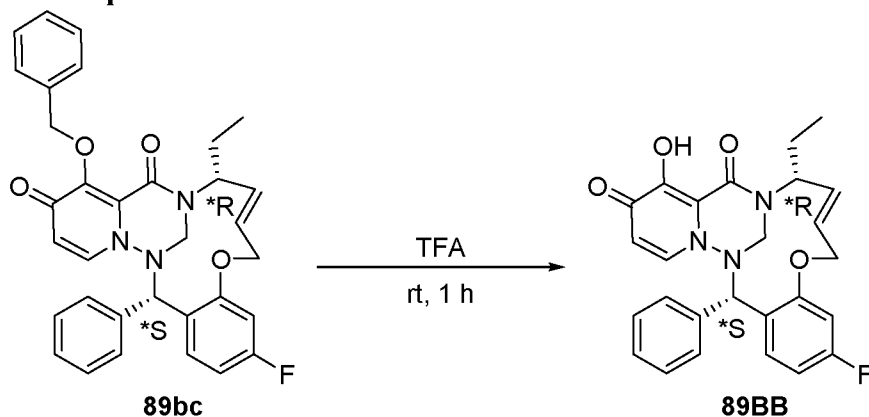
Compound **89AA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.05 (dd, *J*=8.5, 6.9 Hz, 1H), 7.00 - 7.19 (m, 8H), 6.23 (br ddd, *J*=15.7, 9.9, 5.4 Hz, 1H), 5.38 - 5.46 (m, 1H), 5.40 (d, *J*=7.6 Hz, 1H), 5.10 (s, 1H), 5.05 - 5.12 (m, 1H), 4.94 (d, *J*=13.6 Hz, 1H), 4.79 (dd, *J*=11.5, 5.5 Hz, 1H), 4.06 - 4.15 (m, 2H), 1.42 - 1.51 (m, 1H), 1.32 - 1.42 (m, 1H), 0.75 (t, *J*=7.4 Hz, 3H).

LC/MS (method LC-C): Rt 2.89 min, MH⁺ 462

[α]_D²⁰: +553.46 ° (c 0.260, DMF)

Chiral HPLC (method HPLC-B): Rt 5.32 min, chiral purity 100%

Synthesis of compound 89BB:

(9^{*R},18^{*S},*E*)-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **89BB**, 38 mg) was obtained using the procedure described for compound **1**.

Compound 89BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.05 (dd, *J*=8.5, 6.9 Hz, 1H), 6.99 - 7.21 (m, 8H), 6.23 (br ddd, *J*=15.5, 9.9, 5.5 Hz, 1H), 5.40 (d, *J*=7.6 Hz, 1H), 5.36 - 5.46 (m, 1H), 5.10 (s, 1H), 5.04 - 5.13 (m, 1H), 4.94 (d, *J*=13.6 Hz, 1H), 4.79 (dd, *J*=11.5, 5.5 Hz, 1H), 4.05 - 4.16 (m, 2H), 1.42 - 1.51 (m, 1H), 1.32 - 1.41 (m, 1H), 0.75 (t, *J*=7.3 Hz, 3H).

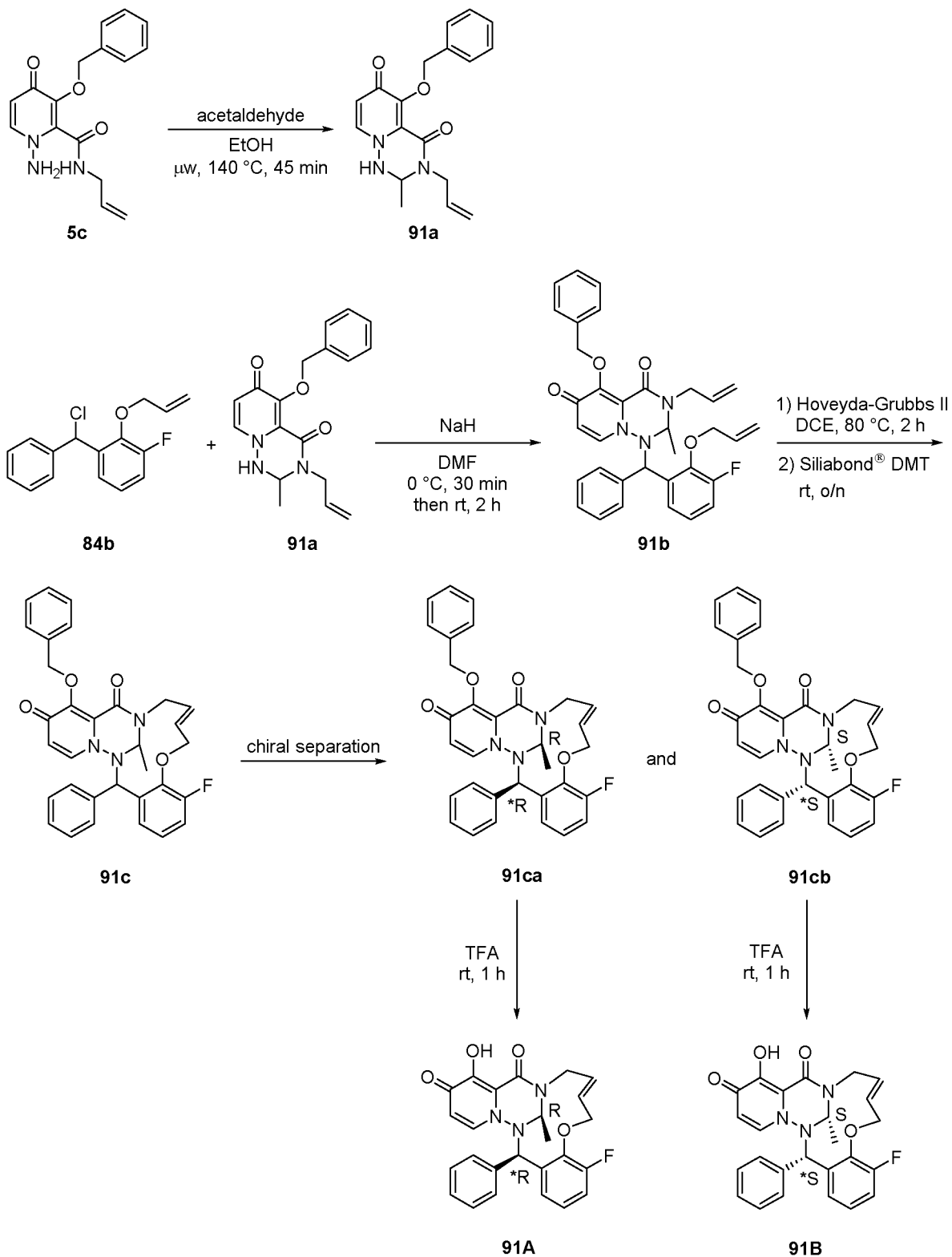
LC/MS (method LC-C): Rt 2.89 min, MH⁺ 462

[α]_D²⁰: -532.62 ° (c 0.282, DMF)

Chiral HPLC (method HPLC-B): Rt 6.95 min, chiral purity 100%

Example 91: synthesis of (18*R*,19*R*,*E*)-4-fluoro-12-hydroxy-19-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **91A**), (18*S*,19*S*,*E*)-4-fluoro-12-hydroxy-19-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **91B**)

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Synthesis of intermediate 91a:

In a microwave a mixture of intermediate **5c** (1.00 g, 3.34 mmol) and acetaldehyde [CAS 75-07-0] (200 μL , 3.56 mmol) in EtOH (15 mL) was stirred at $140\text{ }^\circ\text{C}$ using a single mode microwave (Biotage[®] Initiator EXP 60) with a power output ranging from 0 to 400

W for 45 min. The mixture was concentrated under vacuum. Purification was carried out by flash chromatography over silica gel (30 μ m, 24 g, CH₂Cl₂/MeOH 97/3 to 94/6) to give 3-allyl-5-(benzyloxy)-2-methyl-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **91a**, 935 mg).

5

Synthesis of intermediate 91b:

3-allyl-1-((2-(allyloxy)-3-fluorophenyl)(phenyl)methyl)-5-(benzyloxy)-2-methyl-2,3-dihydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-4,6-dione (intermediate **91b**, 1.20 g) was obtained using the procedure described for intermediate **2d**.

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Synthesis of intermediate 91c:

(*E*)-12-(benzyloxy)-4-fluoro-19-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (intermediate **91c**, 1.22 g) was obtained using the procedure described for intermediate **1f**. Crude intermediate **91c** was purified by flash chromatography over silica gel (30 μ m, 40 g, CH₂Cl₂/MeOH from 97/3 to 95/5). A second purification was performed via reverse phase (Stationary phase: YMC-actus Triart C18 10 μ m 30*150mm, mobile phase gradient: 0.2% aq. NH₄HCO₃/CH₃CN from 50/50 to 30/70) to afford intermediate **91c** (344 mg).

15

The enantiomers were separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5 μ m 250*30mm, Mobile phase: 60% CO₂, 40% EtOH) to give the first eluted enantiomer **91ca** (154 mg) and the second eluted enantiomer **91cb** (159 mg).

20

Synthesis of compound 91A:

(18**R*,19**R,E*)-4-fluoro-12-hydroxy-19-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **91A**, 81 mg) was obtained using the procedure described for compound **1**.

25

Compound 91A:

¹H NMR (500 MHz, DMSO-*d*₆, 77°C) δ ppm 7.87 (d, *J*=7.9 Hz, 1H), 7.37 (td, *J*=8.0, 5.5 Hz, 1H), 7.25 - 7.32 (m, 1H), 7.10 - 7.21 (m, 6H), 6.23 (dt, *J*=15.6, 7.6 Hz, 1H), 5.92 - 6.00 (m, 1H), 5.51 (d, *J*=7.6 Hz, 1H), 5.25 (s, 1H), 4.75 - 4.86 (m, 2H), 4.52 (q, *J*=6.3 Hz, 1H), 4.24 (br dd, *J*=10.7, 9.1 Hz, 1H), 3.25 (dd, *J*=13.9, 8.2 Hz, 1H), 1.34 (d, *J*=6.3 Hz, 3H).

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LC/MS (method LC-C): Rt 2.66 min, MH⁺ 448
[α]_D²⁰: -643.42 ° (c 0.152, DMF)

35

Synthesis of compound 91B:

(18*S,19*S,E)-4-fluoro-12-hydroxy-19-methyl-18-phenyl-6,9-dihydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **91B**, 16 mg) was obtained using the procedure described for compound **1**.

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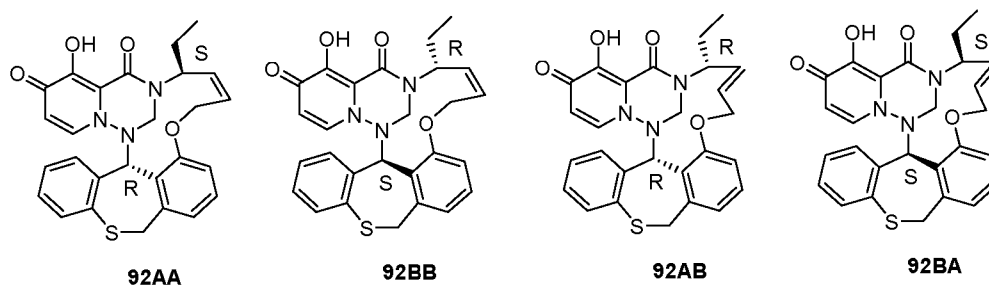
Compound 91B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.90 (br d, *J*=7.6 Hz, 1H), 7.40 (br td, *J*=8.0, 5.4 Hz, 1H), 7.31 - 7.37 (m, 1H), 7.26 (br d, *J*=7.6 Hz, 1H), 7.07 - 7.22 (m, 5H), 6.22 (br s, 1H), 5.98 (br s, 1H), 5.53 (d, *J*=7.6 Hz, 1H), 5.21 (br s, 1H), 4.79 (br dd, *J*=13.7, 4.3 Hz, 2H), 4.52 (q, *J*=6.3 Hz, 1H), 4.24 (br s, 1H), 3.24 - 3.30 (m, 1H), 1.33 (d, *J*=6.3 Hz, 3H).
LC/MS (method LC-C): Rt 2.66 min, MH⁺ 448
[α]_D²⁰: +626.43 ° (c 0.140, DMF)

10

Example 92: synthesis of (13*S*,21*aR*,*Z*)-13-ethyl-16-hydroxy-6,10,13,21*a*-tetrahydro-7,8-(epiprop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **92AA**), (13*R*,21*aS*,*Z*)-13-ethyl-16-hydroxy-6,10,13,21*a*-tetrahydro-7,8-(epiprop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **92BB**), (9*R*,17*aR*,*E*)-9-ethyl-12-hydroxy-2,6,9,17*a*-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **92AB**) and (9*S*,17*aS*,*E*)-9-ethyl-12-hydroxy-2,6,9,17*a*-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-*c*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **92BA**)

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Compounds **92AA**, **92BB**, **92AB** and **92BA** were synthesized according to the procedures described in example **89** starting from intermediates **37c** and **39e**.

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Compound 92AA:

LC/MS (method LC-C): Rt 3.01 min, MH⁺ 488.3
[α]_D²⁰: +148.4 ° (c 0.128, DMF)

Chiral HPLC (method HPLC-B): Rt 3.83 min, chiral purity 100%

Compound 92BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.88 - 12.18 (m, 1 H) 7.41 (t, *J*=7.9 Hz, 1 H)
5 7.20 (d, *J*=7.9 Hz, 1 H) 7.04 - 7.16 (m, 4 H) 6.74 - 6.85 (m, 1 H) 6.53 (d, *J*=7.3 Hz, 1 H)
6.42 - 6.51 (m, 1 H) 6.24 (dt, *J*=10.6, 7.0 Hz, 1 H) 6.07 (s, 1 H) 5.71 (d, *J*=13.6 Hz, 1 H)
5.60 (d, *J*=7.6 Hz, 1 H) 5.17 (d, *J*=13.2 Hz, 1 H) 4.79 (dd, *J*=10.1, 6.6 Hz, 1 H)
4.38 - 4.46 (m, 1 H) 4.36 (d, *J*=13.2 Hz, 1 H) 3.74 - 3.90 (m, 2 H) 1.90 (br dd, *J*=13.9, 6.6 Hz, 1 H) 1.73 - 1.84 (m, 1 H) 0.82 (t, *J*=7.4 Hz, 3 H)

10 LC/MS (method LC-C): Rt 3.00 min, MH⁺ 488

[α]_D²⁰: -144.92 ° (c 0.118, DMF)

Chiral HPLC (method HPLC-B): Rt 5.13 min, chiral purity 99.6%

Compound 92AB:

15 LC/MS (method LC-C): Rt 2.88 min, MH⁺ 488

[α]_D²⁰: +488.89° (c 0.108, DMF)

Chiral HPLC (method HPLC-B): Rt 6.55 min, chiral purity 100%

Compound 92BA:

20 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.42 (t, *J*=7.9 Hz, 1 H) 7.34 (d, *J*=7.9 Hz, 1 H)
7.19 (dd, *J*=13.1, 7.7 Hz, 2 H) 7.08 - 7.14 (m, 1 H) 7.01 - 7.07 (m, 1 H) 6.79 - 6.91 (m, 2 H)
6.29 - 6.42 (m, 1 H) 5.81 (d, *J*=13.2 Hz, 1 H) 5.62 (d, *J*=7.9 Hz, 1 H) 5.50 - 5.59 (m, 1 H)
5.34 (s, 1 H) 5.18 (q, *J*=7.1 Hz, 1 H) 5.06 (d, *J*=13.6 Hz, 1 H) 4.89 (dd, *J*=11.2, 5.5 Hz, 1 H)
4.20 - 4.36 (m, 2 H) 3.87 (d, *J*=13.6 Hz, 1 H) 1.39 - 1.62 (m, 2 H)
25 0.82 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 2.88 min, MH⁺ 488

[α]_D²⁰: -510.78 ° (c 0.102, DMF)

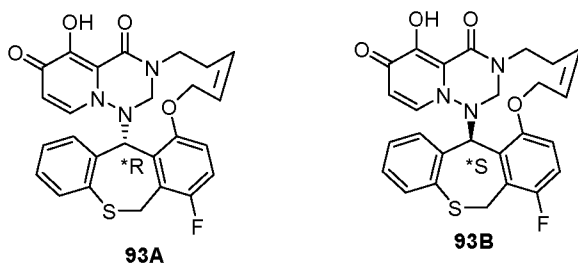
Chiral HPLC (method HPLC-B): Rt 10.1 min, chiral purity 100%

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Example 93: synthesis of (1*R,13Z)-20-fluoro-7-hydroxy-16-oxa-23-thia-2,3,10-triazahexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6 (Compound **93A**) and (1*SR,13Z)-20-fluoro-7-hydroxy-16-oxa-23-thia-2,3,10-

35 triazahexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6 (Compound **93B**)

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Compounds **93A** and **93B** were synthesized according to the procedures described in example **37** starting from intermediate 10-(allyloxy)-11-chloro-7-fluoro-6,11-dihydrodibenzo[b,e]thiepine.

Compound 93A:

LC/MS (method LC-C): Rt 2.85 min, MH^+ 492

$[\alpha]_D^{20}$: +197.09 ° (c 0.103, DMF)

Chiral HPLC (method HPLC-B): Rt 4.41 min, chiral purity 100%

Compound 93B:

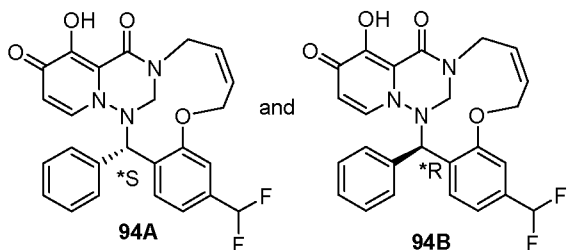
^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.25 (t, $J=9.1$ Hz, 1 H) 7.16 (d, $J=7.6$ Hz, 1 H) 7.04 - 7.09 (m, 1 H) 6.98 - 7.04 (m, 2 H) 6.77 (t, $J=7.3$ Hz, 1 H) 6.53 (d, $J=7.3$ Hz, 1 H) 5.96 - 6.04 (m, 2 H) 5.86 - 5.93 (m, 1 H) 5.44 - 5.56 (m, 2 H) 4.89 (d, $J=13.2$ Hz, 1 H) 4.38 - 4.52 (m, 2 H) 4.33 (d, $J=13.2$ Hz, 1 H) 4.14 - 4.22 (m, 1 H) 3.94 (d, $J=13.9$ Hz, 1 H) 2.77 (br d, $J=14.2$ Hz, 1 H) 2.15 - 2.26 (m, 1 H) 2.04 - 2.15 (m, 1 H)

LC/MS (method LC-C): Rt 2.85 min, MH^+ 492

$[\alpha]_D^{20}$: -185.38 ° (c 0.13, DMF)

Chiral HPLC (method HPLC-B): Rt 6.28 min, chiral purity 100%

Example 94: synthesis of (18*S,Z)-3-(difluoromethyl)-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **94A**) and (18*R,Z)-3-(difluoromethyl)-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **94B**)



Compounds **94A** and **94B** were synthesized according to the procedures described in example **5** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-4-(difluoromethyl)benzene.

5 Compound 94A:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.26 (d, $J=7.9$ Hz, 1 H) 7.56 (d, $J=7.9$ Hz, 1 H) 7.46 (s, 1 H) 7.26 (br d, $J=7.9$ Hz, 1 H) 6.92 – 7.22 (m, 6 H) 6.06 – 6.24 (m, 1 H) 5.85 – 6.04 (m, 1 H) 5.49 (d, $J=7.9$ Hz, 1 H) 5.35 (s, 1 H) 5.12 (d, $J=13.9$ Hz, 1 H) 4.71 – 4.89 (m, 2 H) 4.31 – 4.41 (m, 1 H) 4.24 (d, $J=13.9$ Hz, 1 H) 3.16 – 3.24 (m, 1 H)

10 LC/MS (method LC-C): Rt 2.59 min, MH^+ 466

$[\alpha]_{\text{D}}^{20}$: -609.86 ° (c 0.142, DMF)

Chiral HPLC (method HPLC-B): Rt 4.79 min, chiral purity 100%

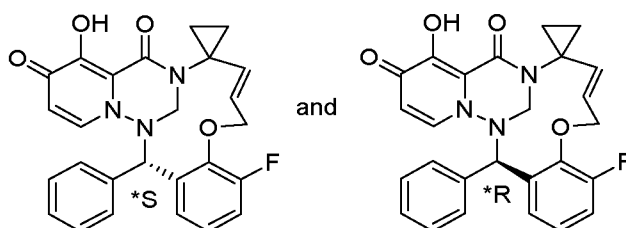
Compound 94B:

15 LC/MS (method LC-C): Rt 2.59 min, MH^+ 466

$[\alpha]_{\text{D}}^{20}$: +569.83 ° (c 0.179, DMF)

Chiral HPLC (method HPLC-B): Rt 4.14 min, chiral purity 100%

Example 95: synthesis of (18'*S,E)-4'-fluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **95A**) and (18'*R,E)-4'-fluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (compound **95B**)



Compounds **95A** and **95B** were synthesized according to the procedures described in example **79** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene **61b**

Compound 95A:

30 LC/MS (method LC-C): Rt 2.76 min, MH^+ 460

$[\alpha]_{\text{D}}^{20}$: +543.93 ° (c 0.107, DMF)

Chiral HPLC (method HPLC-A): Rt 6.25 min, chiral purity 100%

Compound 95B:

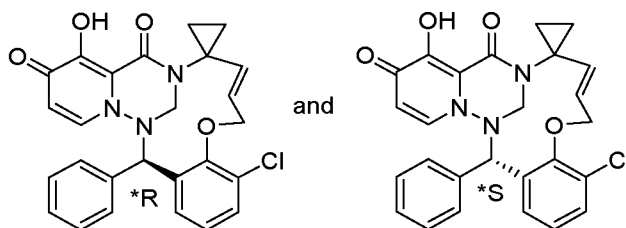
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.88 (br d, *J*=7.9 Hz, 1 H) 7.37 - 7.43 (m, 1 H) 7.30 - 7.37 (m, 1 H) 7.13 - 7.30 (m, 6 H) 6.30 - 6.41 (m, 1 H) 5.80 (br d, *J*=15.1 Hz, 1 H) 5.51 (d, *J*=7.6 Hz, 1 H) 5.37 (s, 1 H) 5.13 (d, *J*=13.6 Hz, 1 H) 4.86 (br dd, *J*=10.7, 6.0 Hz, 1 H) 4.22 (d, *J*=13.6 Hz, 1 H) 4.16 (br t, *J*=10.1 Hz, 1 H) 1.53 (dt, *J*=9.8, 6.8 Hz, 1 H) 1.18 (dt, *J*=9.6, 6.5 Hz, 1 H) 0.84 - 0.93 (m, 1 H) 0.69 - 0.78 (m, 1 H)

LC/MS (method LC-C): Rt 2.76 min, MH⁺ 460

[α]_D²⁰: -576.12 ° (c 0.134, DMF)

Chiral HPLC (method HPLC-A): Rt 7.93 min, chiral purity 100%

Example 96: synthesis of (18'^{*}R,E)-4'-chloro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **96A**) and (18'^{*}S,E)-4'-fluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (compound **96B**)



Compounds **96A** and **96B** were synthesized according to the procedures described in example 79 starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-chlorobenzene **75b**

Compound 96A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.04 (d, *J*=7.6 Hz, 1 H) 7.55 (dd, *J*=7.9, 1.3 Hz, 1 H) 7.41 (t, *J*=8.0 Hz, 1 H) 7.14 - 7.27 (m, 6 H) 6.42 (ddd, *J*=14.9, 9.2, 6.1 Hz, 1 H) 5.71 (br d, *J*=15.1 Hz, 1 H) 5.50 (d, *J*=7.9 Hz, 1 H) 5.40 (s, 1 H) 5.16 (d, *J*=13.9 Hz, 1 H) 4.86 (dd, *J*=11.0, 5.7 Hz, 1 H) 4.22 - 4.36 (m, 2 H) 1.51 - 1.61 (m, 1 H) 1.19 (dt, *J*=9.5, 6.5 Hz, 1 H) 0.86 - 0.94 (m, 1 H) 0.71 - 0.79 (m, 1 H)

LC/MS (method LC-C): Rt 2.95 min, MH⁺ 476

[α]_D²⁰: -549.22 ° (c 0.128, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 96B:LC/MS (method LC-C): Rt 2.95 min, MH^+ 476 $[\alpha]_D^{20}$: +530.4° (c 0.125, DMF)Chiral HPLC (method HPLC-A and B): **No separation observed**

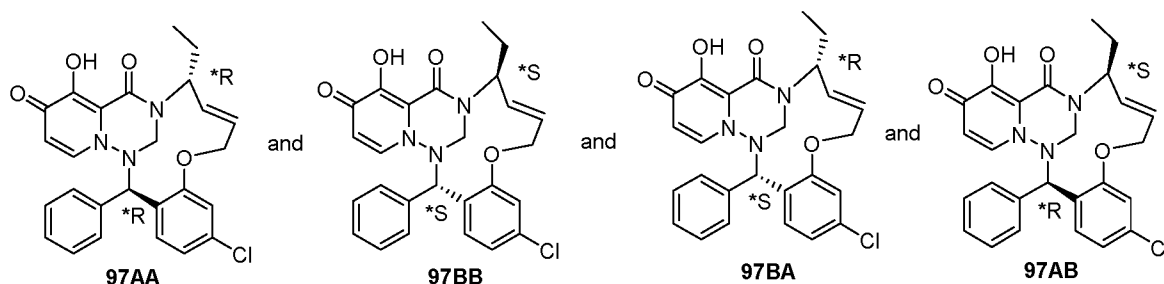
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Example 97: synthesis of (9R,18R,E)-3-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **97AA**) and (9S,18S,E)-3-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **97BB**) and (9R,18S,E)-3-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **97BA**) and (9S,18R,E)-3-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-

11,13-dione (Compound **97AB**)



Compounds **97AA**, **97BB**, **97BA** and **97AB** were synthesized according to the procedures described in example **39** starting from intermediate 2-(allyloxy)-4-chloro-1-(chloro(phenyl)methyl)benzene **72b**.

Compound 97AA:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 8.04 (d, $J=8.5$ Hz, 1 H) 7.37 (dd, $J=8.4, 2.0$ Hz, 1 H) 7.26 (d, $J=1.9$ Hz, 1 H) 6.96 - 7.21 (m, 6 H) 6.22 (ddd, $J=15.6, 9.9, 5.4$ Hz, 1 H) 5.37 - 5.51 (m, 2 H) 5.04 - 5.16 (m, 2 H) 4.95 (d, $J=13.6$ Hz, 1 H) 4.80 (dd, $J=11.5, 5.5$ Hz, 1 H) 4.14 (d, $J=13.9$ Hz, 1 H) 4.09 (br t, $J=10.9$ Hz, 1 H) 1.33 - 1.52 (m, 2 H) 0.75 (t, $J=7.3$ Hz, 3 H)

LC/MS (method LC-C): Rt 3.12 min, MH^+ 478 $[\alpha]_D^{20}$: -677.24° (c 0.123, DMF)

Chiral HPLC (method HPLC-B): Rt 7.21 min, chiral purity 100%

Compound 97BB:LC/MS (method LC-C): Rt 3.12 min, MH⁺ 478[α]_D²⁰: +631.94° (c 0.144, DMF)

Chiral HPLC (method HPLC-B): Rt 5.37 min, chiral purity 100%

5

Compound 97BA:LC/MS (method LC-C): Rt 3.14 min, MH⁺ 478[α]_D²⁰: +704.50° (c 0.111, DMF)

Chiral HPLC (method HPLC-A): Rt 4.41 min, chiral purity 100%

10

Compound 97AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.09 (d, *J*=8.5 Hz, 1 H) 7.38 (d, *J*=1.9 Hz, 1 H) 7.34 (dd, *J*=8.5, 1.9 Hz, 1 H) 7.26 (d, *J*=7.6 Hz, 1 H) 6.95 - 7.21 (m, 5 H) 6.33 (br dd, *J*=15.1, 10.1 Hz, 1 H) 5.80 (dt, *J*=15.3, 7.5 Hz, 1 H) 5.42 (d, *J*=7.6 Hz, 1 H) 5.33 (s, 1 H) 5.09 (d, *J*=13.9 Hz, 1 H) 4.55 (br d, *J*=7.9 Hz, 2 H) 4.12 (d, *J*=14.2 Hz, 1 H) 2.18 - 2.28 (m, 1 H) 1.99 - 2.13 (m, 1 H) 0.78 (t, *J*=7.3 Hz, 3 H)

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LC/MS (method LC-C): Rt 3.14 min, MH⁺ 478[α]_D²⁰: -718.25° (c 0.137, DMF)

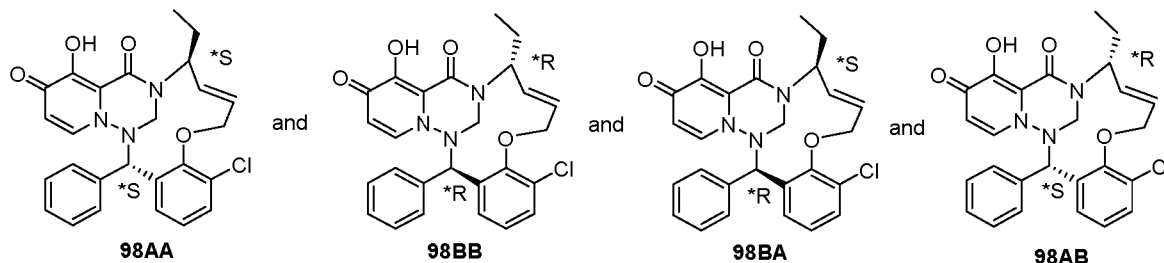
Chiral HPLC (method HPLC-A): Rt 5.39 min, chiral purity 100%

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Example 98: synthesis of (9*S,18*S,E)-4-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **98AA**) and (9*R,18*R,E)-4-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **98BB**) and (9*S,18*R,E)-4-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **98BA**) and (9*R,18*S,E)-4-chloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **98AB**)

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Compounds **98AA**, **98BB**, **98BA** and **98AB** were synthesized according to the procedures described in example **39** starting from intermediate 2-(allyloxy)-1-chloro-3-(chloro(phenyl)methyl)benzene **75b**.

5 **Compound 98AA:**

LC/MS (method LC-C): Rt 3.10 min, MH⁺ 478.2

[α]_D²⁰: +585.32 ° (c 0.218, DMF)

Chiral HPLC (method HPLC-A): Rt 7.57 min, chiral purity 100%

10 **Compound 98BB:**

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.10 (dd, *J*=7.9, 1.3 Hz, 1 H) 7.58 (dd, *J*=7.9, 1.6 Hz, 1 H) 7.42 (t, *J*=7.9 Hz, 1 H) 7.25 (d, *J*=7.9 Hz, 1 H) 6.99 - 7.21 (m, 5 H) 6.40 (ddd, *J*=15.4, 10.4, 5.0 Hz, 1 H) 5.50 - 5.56 (m, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.26 (s, 1 H) 5.18 (q, *J*=7.6 Hz, 1 H) 5.08 (d, *J*=13.6 Hz, 1 H) 4.87 (dd, *J*=11.7, 5.0 Hz, 1 H) 4.26 (d, *J*=13.6 Hz, 1 H) 4.08 (br t, *J*=11.0 Hz, 1 H) 1.40 - 1.60 (m, 2 H) 0.83 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.10min, MH⁺ 478

[α]_D²⁰: -587.58 ° (c 0.161, DMF)

Chiral HPLC (method HPLC-A): Rt 6.78 min, chiral purity 100%

20 **Compound 98BA:**

LC/MS (method LC-C): Rt 3.13 min, MH⁺ 478

[α]_D²⁰: +620.73 ° (c 0.164, DMF)

Chiral HPLC (method HPLC-A): Rt 5.81 min, chiral purity 100%

25 **Compound 98AB:**

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.13 (br d, *J*=7.6 Hz, 1 H) 7.53 (dd, *J*=7.9, 1.3 Hz, 1 H) 7.37 - 7.45 (m, 1 H) 7.32 (d, *J*=7.6 Hz, 1 H) 7.16 (br d, *J*=2.8 Hz, 5 H) 6.44 (br s, 1 H) 5.84 (br s, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.47 (s, 1 H) 5.23 (d, *J*=13.9 Hz, 1 H) 4.75 - 4.86 (m, 1 H) 4.60 - 4.68 (m, 1 H) 4.27 (d, *J*=13.9 Hz, 1 H) 3.44 - 3.51 (m, 1 H) 2.29 - 2.37 (m, 1 H) 2.10 - 2.20 (m, 1 H) 0.87 (t, *J*=7.4 Hz, 3 H)

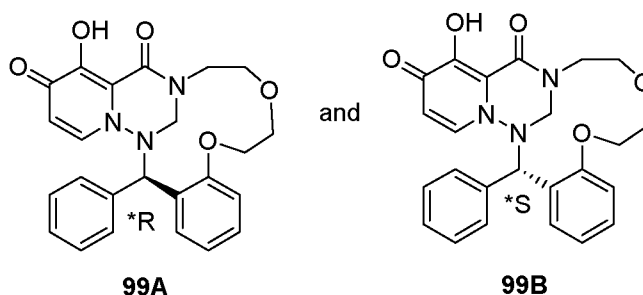
LC/MS (method LC-C): Rt 3.13 min, MH⁺ 478

[α]_D²⁰: -680.36° (c 0.168, DMF)

Chiral HPLC (method HPLC-A): Rt 6.59 min, chiral purity 100%

35 Example 99: synthesis of (2*R)-18-hydroxy-2-phenyl-9,12-dioxa-1,15,22-triazatetracyclo[13.7.1.03,8.017,22]tricos-3,5,7,17,20-pentaene-16,19-dione (Compound **99A**) and (2*S)-18-hydroxy-2-phenyl-9,12-dioxa-1,15,22-

triazatetracyclo[13.7.1.03,8.017,22]tricos-3,5,7,17,20-pentaene-16,19-dione
(compound **99B**)



Compounds **99A** and **99B** were synthesized according to the procedures described in example **80** starting from intermediates 5-(benzyloxy)-3-(2-(2-((tert-butyl)diphenylsilyl)oxy)ethoxy)ethyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione and **5a**.

Compound 99A:

LC/MS (method LC-C): Rt 2.43 min, MH⁺ 434

[α]_D²⁰: +262.6 ° (c 0.123, DMF)

Chiral HPLC (method HPLC-A): Rt 5.30 min, chiral purity 89.24%

Compound 99B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.12 (dd, *J*=7.7, 1.1 Hz, 1 H) 7.29 - 7.39 (m, 2 H) 7.21 (t, *J*=7.6 Hz, 1 H) 7.05 - 7.18 (m, 6 H) 6.14 (s, 1 H) 5.45 (d, *J*=7.9 Hz, 1 H) 5.08 (d, *J*=12.9 Hz, 1 H) 4.33 - 4.42 (m, 1 H) 4.26 (d, *J*=12.9 Hz, 1 H) 4.16 - 4.23 (m, 1 H) 4.06 - 4.14 (m, 1 H) 3.82 (td, *J*=9.5, 2.2 Hz, 1 H) 3.68 - 3.76 (m, 1 H) 3.52 - 3.63 (m, 2 H) 3.02 (ddd, *J*=14.3, 9.1, 2.4 Hz, 1 H)

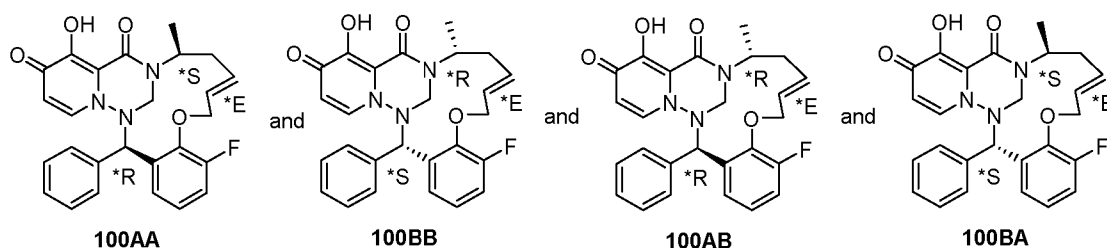
LC/MS (method LC-C): Rt 2.43 min, MH⁺ 434

[α]_D²⁰: -202.86 ° (c 0.140, DMF)

Chiral HPLC (method HPLC-A): Rt 5.01 min, chiral purity 76.75%

Example 100: synthesis of (2^{*R},9^{*S},^{*E})-33-fluoro-15-hydroxy-9-methyl-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **100AA**), (2^{*R},9^{*R},^{*E})-33-fluoro-15-hydroxy-9-methyl-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **100AB**), (2^{*S},9^{*S},^{*E})-33-fluoro-15-hydroxy-9-methyl-2-phenyl-

12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **100BA**) and (2*S,9*R,*E)-33-fluoro-15-hydroxy-9-methyl-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **100BB**)



Compounds **100AA**, **100BB**, **100BA** and **100AB** were synthesized according to the procedures described in example **29** starting from intermediates 5-(benzyloxy)-3-(pent-4-en-2-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione **29c** and 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene **61b**.

Compound **100AA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.77 (d, *J*=7.6 Hz, 1 H) 7.28 - 7.40 (m, 2 H) 7.09 - 7.27 (m, 4 H) 7.06 (d, *J*=7.6 Hz, 1 H) 6.84 - 7.02 (m, 1 H) 6.03 (ddd, *J*=15.2, 9.7, 5.7 Hz, 1 H) 5.86 (s, 1 H) 5.61 - 5.71 (m, 1 H) 5.39 (d, *J*=7.6 Hz, 1 H) 5.21 (d, *J*=13.2 Hz, 1 H) 4.73 (dd, *J*=12.0, 5.7 Hz, 1 H) 4.30 (d, *J*=13.2 Hz, 1 H) 4.11 (t, *J*=10.9 Hz, 1 H) 3.18 - 3.26 (m, 2 H) 2.07 - 2.15 (m, 1 H) 1.40 (d, *J*=6.0 Hz, 3 H)

LC/MS (method LC-C): Rt 2.90 min, MH⁺ 462

[α]_D²⁰: -393.65 ° (c 0.126, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound **100AB**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.91 (d, *J*=7.6 Hz, 1 H) 7.37 (td, *J*=8.0, 5.4 Hz, 1 H) 7.29 - 7.33 (m, 1 H) 7.27 (d, *J*=7.6 Hz, 1 H) 6.92 - 7.25 (m, 5 H) 5.78 (dt, *J*=15.6, 7.6 Hz, 1 H) 5.68 (s, 1 H) 5.48 - 5.58 (m, 1 H) 5.40 (d, *J*=7.9 Hz, 1 H) 5.00 (d, *J*=12.9 Hz, 1 H) 4.86 (ddd, *J*=10.8, 6.5, 4.4 Hz, 1 H) 4.69 (dd, *J*=11.2, 6.8 Hz, 1 H) 4.15 - 4.26 (m, 2 H) 2.21 (ddd, *J*=17.6, 10.6, 7.1 Hz, 1 H) 1.11 (d, *J*=6.9 Hz, 3 H)

LC/MS (method LC-C): Rt 2.84 min, MH⁺ 462

[α]_D²⁰: -402.94° (c 0.102, DMF)

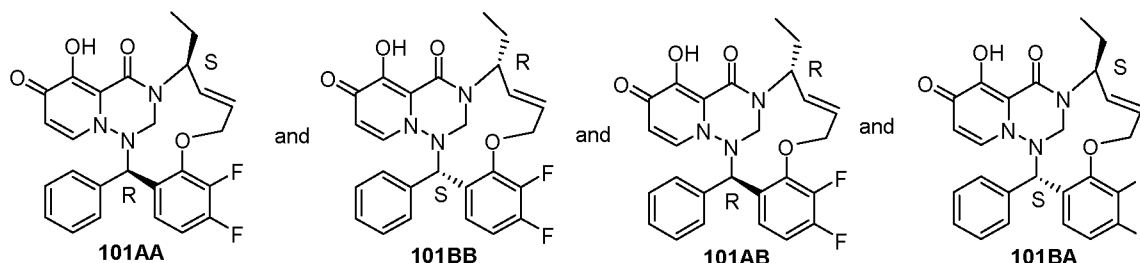
Chiral HPLC (method HPLC-A): Rt 5.89 min, chiral purity 100%

Compound 100BA:LC/MS (method LC-C): Rt 2.84 min, MH^+ 462 $[\alpha]_D^{20}$: +374.15 ° (c 0.147, DMF)

Chiral HPLC (method HPLC-A): Rt 8.28 min, chiral purity 100%

Compound 100BB:LC/MS (method LC-C): Rt 2.90 min, MH^+ 462 $[\alpha]_D^{20}$: +385.04 ° (c 0.127, DMF)Chiral HPLC (method HPLC-A and B): **No separation observed**

Example 101: synthesis of (9S,18R,E)-9-ethyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **101AA**) and (9R,18S,E)-9-ethyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **101BB**) and (9R,18R,E)-9-ethyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **101AB**) and (9S,18S,E)-9-ethyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **101BA**)



Compounds **101AA**, **101BB**, **101BA** and **101AB** were synthesized according to the procedures described in example **39** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene **74c**.

Compound 101AA:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 10.70 - 11.53 (m, 1 H) 7.94 (br t, $J=6.8$ Hz, 1 H) 7.45 - 7.54 (m, 1 H) 7.01 - 7.30 (m, 6 H) 6.37 (ddd, $J=15.4, 10.1, 5.4$ Hz, 1 H) 5.67 (br dd, $J=15.4, 6.3$ Hz, 1 H) 5.48 (d, $J=7.6$ Hz, 1 H) 5.12 - 5.25 (m, 2 H) 5.05 (d, $J=13.6$ Hz, 1 H) 4.92 (dd, $J=11.3, 5.4$ Hz, 1 H) 4.23 (d, $J=13.6$ Hz, 1 H) 4.08 (br t, $J=10.9$ Hz, 1 H) 1.39 - 1.64 (m, 2 H) 0.83 (t, $J=7.3$ Hz, 3 H)

LC/MS (method LC-C): Rt 2.98 min, MH^+ 480

$[\alpha]_D^{20}$: -545.62° (c 0.217, DMF)

Chiral HPLC (method HPLC-B): Rt 5.88 min, chiral purity 100%

5 **Compound 101AB:**

^1H NMR (500 MHz, DMSO- d_6) δ ppm 9.89 - 11.09 (m, 1 H) 7.99 (br t, $J=6.8$ Hz, 1 H) 7.41 - 7.57 (m, 1 H) 7.32 (d, $J=7.6$ Hz, 1 H) 6.91 - 7.26 (m, 5 H) 6.39 - 6.58 (m, 1 H) 5.87 - 6.03 (m, 1 H) 5.49 (d, $J=7.6$ Hz, 1 H) 5.37 (s, 1 H) 5.20 (d, $J=13.9$ Hz, 1 H) 4.70 (br t, $J=10.2$ Hz, 1 H) 4.58 (br dd, $J=10.2, 5.2$ Hz, 1 H) 4.22 (d, $J=13.9$ Hz, 1 H) 3.40 - 3.48 (m, 1 H) 2.27 - 2.38 (m, 1 H) 2.08 - 2.24 (m, 1 H) 0.87 (t, $J=7.4$ Hz, 3 H)

LC/MS (method LC-C): Rt 3.04 min, MH^+ 480

$[\alpha]_D^{20}$: -683.61° (c 0.244, DMF)

Chiral HPLC (method HPLC-A): Rt 7.01 min, chiral purity 100%

15 **Compound 101BA:**

LC/MS (method LC-C): Rt 3.05 min, MH^+ 480

$[\alpha]_D^{20}$: +623.44° (c 0.209, DMF)

Chiral HPLC (method HPLC-A): Rt 4.42 min, chiral purity 100%

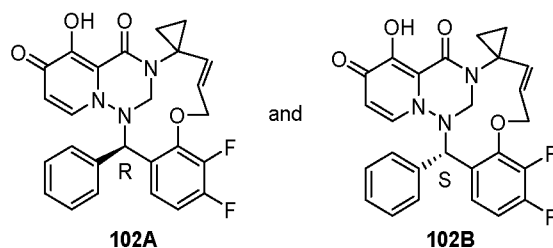
20 **Compound 101BB:**

LC/MS (method LC-C): Rt 2.99 min, MH^+ 480

$[\alpha]_D^{20}$: +568.75° (c 0.112, DMF)

Chiral HPLC (method HPLC-B): Rt 4.41 min, chiral purity 100%

- 25 Example 102: synthesis of (18'R,E)-3',4'-difluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **102A**), (18'S,E)-3',4'-difluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **102B**)



Compounds **102A** and **102B** were synthesized according to the procedures described in example **79** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene **74c**.

5 Compound 102A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.90 (br t, *J*=7.1 Hz, 1 H) 7.47 (br d, *J*=8.2 Hz, 1 H) 6.99 - 7.37 (m, 6 H) 6.37 (dt, *J*=14.5, 7.6 Hz, 1 H) 5.94 (br d, *J*=14.8 Hz, 1 H) 5.50 (d, *J*=7.6 Hz, 1 H) 5.32 (s, 1 H) 5.11 (br d, *J*=13.9 Hz, 1 H) 4.90 (br dd, *J*=10.9, 6.1 Hz, 1 H) 4.16 - 4.35 (m, 2 H) 1.52 (br dd, *J*=5.8, 2.7 Hz, 1 H) 1.13 - 1.28 (m, 1 H) 0.82 - 0.97 (m, 1 H) 0.69 - 0.78 (m, 1 H)

LC/MS (method LC-C): Rt 2.90 min, MH⁺ 478

[α]_D²⁰: -575.36 ° (c 0.138, DMF)

Chiral HPLC (method HPLC-B): Rt 5.70 min, chiral purity 100%

15 Compound 102B:

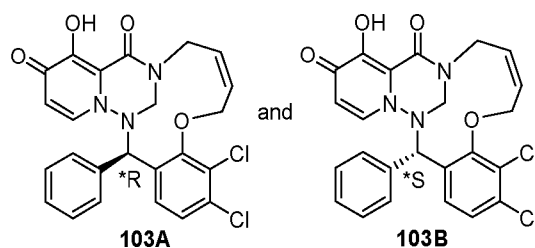
LC/MS (method LC-C): Rt 2.87 min, MH⁺ 478

[α]_D²⁰: +563.28 ° (c 0.128, DMF)

Chiral HPLC (method HPLC-B): Rt 4.64 min, chiral purity 100%

20 Example 103: synthesis of (18^{*R,Z})-3,4-dichloro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **103A**) and (18^{*S,Z})-3,4-dichloro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **103B**)

25



Compounds **103A** and **103B** were synthesized according to the procedures described in example **5** starting from intermediate 2-(allyloxy)-3,4-dichloro-1-(chloro(phenyl)methyl) benzene (synthesized as **74c** from 3,4-dichloro-2-hydroxybenzaldehyde [CAS 23602-61-1]).

30

Compound 103A:LC/MS (method LC-C): Rt 3.01 min, MH⁺ 484[α]_D²⁰: +709.83° (c 0.173, DMF)

Chiral HPLC (method HPLC-B): Rt 5.22 min, chiral purity 100%

5

Compound 103B:

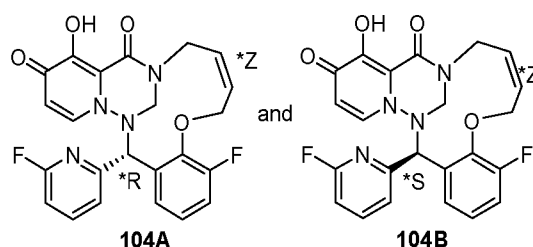
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.11 (br d, *J*=8.5 Hz, 1 H) 7.71 (d, *J*=8.5 Hz, 1 H) 6.98 - 7.32 (m, 6 H) 6.28 (br s, 1 H) 5.97 (br s, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.27 (br s, 1 H) 5.16 (d, *J*=13.6 Hz, 1 H) 4.83 (br dd, *J*=13.6, 4.4 Hz, 2 H) 4.26 - 4.51 (m, 2 H)

10 3.20 (br dd, *J*=14.0, 7.7 Hz, 1 H)LC/MS (method LC-C): Rt 3.01 min, MH⁺ 484[α]_D²⁰: -666.42° (c 0.134, DMF)

Chiral HPLC (method HPLC-B): Rt 5.79 min, chiral purity 99.31%

15

Example 104: synthesis of (18^{*}R,^{*}Z)-4-fluoro-18-(6-fluoropyridin-2-yl)-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **104A**) and (18^{*}S,^{*}Z)-4-fluoro-18-(6-fluoropyridin-2-yl)-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **104B**)



25 Compounds **104A** and **104B** were synthesized according to the procedures described in example 5 starting from intermediate 2-((2-(allyloxy)-3-fluorophenyl)chloromethyl)-6-fluoropyridine (synthesized as **76c** from 1-bromo-3-fluoro-2-(2-propen-1-yloxy)-benzene [CAS 1010422-27-1]).

Compound 104A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.90 (br d, *J*=7.3 Hz, 1 H) 7.85 (q, *J*=8.2 Hz, 1 H) 7.33 - 7.46 (m, 2 H) 7.21 - 7.28 (m, 1 H) 7.15 (d, *J*=7.6 Hz, 1 H) 7.06 (dd, *J*=8.2, 2.2 Hz, 1 H) 6.16 - 6.33 (m, 1 H) 5.96 (br s, 1 H) 5.59 (d, *J*=7.9 Hz, 1 H) 5.41 (s, 1 H)

30

5.14 (d, $J=13.9$ Hz, 1 H) 4.81 (br dd, $J=13.6, 4.7$ Hz, 2 H) 4.25 (d, $J=13.9$ Hz, 2 H)
3.21 (br dd, $J=14.0, 8.0$ Hz, 1 H)

LC/MS (method LC-C): Rt 2.46 min, MH^+ 453

$[\alpha]_D^{20}$: -622.99 ° (c 0.087, DMF)

5 Chiral HPLC (method HPLC-A): Rt 6.78 min, chiral purity 100%

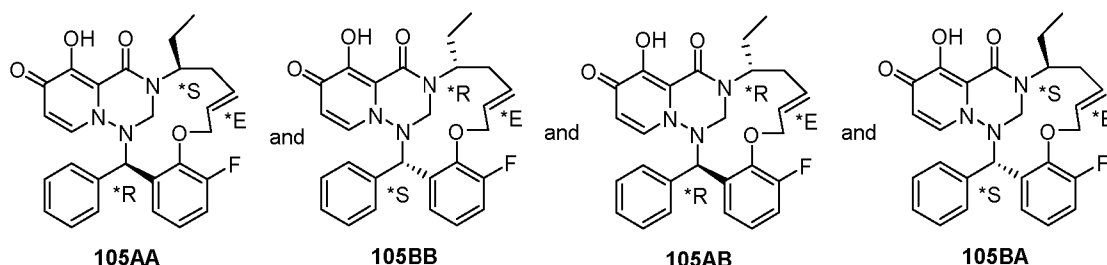
Compound 104B:

LC/MS (method LC-C): Rt 2.46 min, MH^+ 453

$[\alpha]_D^{20}$: +637.18 ° (c 0.078, DMF)

10 Chiral HPLC (method HPLC-A): Rt 5.41 min, chiral purity 100%

Example 105: synthesis of (2*R,9*S,*E)-9-ethyl-33-fluoro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-1H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **105AA**), (2*R,9*R,*E)-9-ethyl-33-fluoro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-1H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **105AB**), (2*S,9*S,*E)-9-ethyl-33-fluoro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-1H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **105BA**) and (2*S,9*R,*E)-9-ethyl-33-fluoro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-1H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (Compound **105BB**)



25 Compounds **105AA**, **105BB**, **105BA** and **105AB** were synthesized according to the procedures described in example **39** starting from intermediates 5-(benzyloxy)-3-(hex-5-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized as **39e** from 5-hexen-3-amine [CAS 239126-98-8]) and 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene **61b**.

Compound 105AA:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.77 (d, $J=7.6$ Hz, 1 H) 7.29 - 7.44 (m, 2 H)

7.19 (br s, 4 H) 7.06 (d, $J=7.6$ Hz, 1 H) 6.84 - 7.01 (m, 1 H) 6.05 (ddd, $J=15.2, 9.9, 5.5$

Hz, 1 H) 5.88 (s, 1 H) 5.64 (ddd, $J=15.4, 10.5, 4.7$ Hz, 1 H) 5.39 (d, $J=7.6$ Hz, 1 H) 5.13 (d, $J=13.2$ Hz, 1 H) 4.72 (dd, $J=12.0, 5.4$ Hz, 1 H) 4.37 (d, $J=13.2$ Hz, 1 H) 4.10 (br t, $J=10.9$ Hz, 1 H) 3.13 - 3.22 (m, 1 H) 2.99 - 3.09 (m, 1 H) 2.15 - 2.25 (m, 1 H) 2.08 (dt, $J=14.1, 7.8$ Hz, 1 H) 1.64 (dt, $J=14.0, 6.7$ Hz, 1 H) 0.81 (t, $J=7.4$ Hz, 3 H)

5

LC/MS (method LC-C): Rt 3.04 min, MH^+ 476

$[\alpha]_D^{20}$: -322.46° (c 0.138, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

10 **Compound 105AB:**

^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.90 (d, $J=7.6$ Hz, 1 H) 7.34 - 7.42 (m, 1 H) 7.27 - 7.33 (m, 2 H) 6.90 - 7.26 (m, 5 H) 5.67 - 5.75 (m, 1 H) 5.65 (s, 1 H) 5.54 - 5.62 (m, 1 H) 5.41 (d, $J=7.6$ Hz, 1 H) 4.96 (d, $J=12.9$ Hz, 1 H) 4.78 (br dd, $J=11.5, 4.6$ Hz, 1 H) 4.67 (dd, $J=11.0, 7.3$ Hz, 1 H) 4.20 - 4.30 (m, 2 H) 2.53 - 2.58 (m, 1 H) 2.14 - 2.27

15 (m, 1 H) 1.45 - 1.53 (m, 2 H) 0.81 (t, $J=7.4$ Hz, 3 H)

LC/MS (method LC-C): Rt 2.98 min, MH^+ 476

$[\alpha]_D^{20}$: -386.61° (c 0.127, DMF)

Chiral HPLC (method HPLC-A): Rt 5.89 min, chiral purity 100%

20

Compound 105BA:

LC/MS (method LC-C): Rt 2.98 min, MH^+ 476

$[\alpha]_D^{20}$: $+418.47^\circ$ (c 0.112, DMF)

Chiral HPLC (method HPLC-A): Rt 8.00 min, chiral purity 100%

25

Compound 105BB:

LC/MS (method LC-C): Rt 3.04 min, MH^+ 476

$[\alpha]_D^{20}$: $+350.00^\circ$ (c 0.150, DMF)

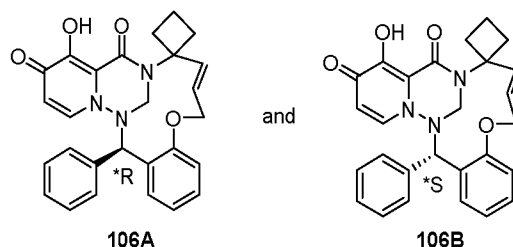
Chiral HPLC (method HPLC-A and B): **No separation observed**

30

Example 106: synthesis of (18' $^*R,E$)-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **106A**), ((18' $^*S,E$)-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **106B**)

35

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Compounds **106A** and **106B** were synthesized according to the procedures described in example **79** starting from intermediate 5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione **146f**.

Compound **106A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.09 (dd, *J*=7.7, 1.1 Hz, 1 H) 7.40 (br dd, *J*=7.9, 1.3 Hz, 1 H) 7.29 - 7.36 (m, 2 H) 7.26 (d, *J*=7.9 Hz, 1 H) 7.04 - 7.22 (m, 5 H) 6.40 (br d, *J*=15.8 Hz, 1 H) 5.91 - 6.05 (m, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.32 (s, 1 H) 5.09 (d, *J*=13.6 Hz, 1 H) 4.70 - 4.79 (m, 1 H) 4.53 (br dd, *J*=10.7, 6.3 Hz, 1 H) 3.79 (d, *J*=13.6 Hz, 1 H) 2.77 - 2.87 (m, 1 H) 2.41 - 2.48 (m, 1 H) 2.01 - 2.10 (m, 1 H) 1.93 - 2.00 (m, 1 H) 1.68 - 1.80 (m, 1 H) 1.52 - 1.65 (m, 1 H)

LC/MS (method LC-C): Rt 2.90 min, MH⁺ 456

[α]_D²⁰: -666.91° (c 0.139, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound **106B**:

LC/MS (method LC-C): Rt 2.90 min, MH⁺ 456

[α]_D²⁰: +686.26° (c 0.182, DMF)

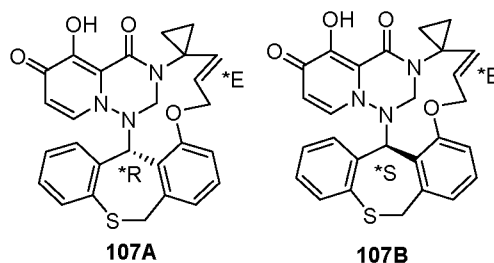
Chiral HPLC (method HPLC-A and B): **No separation observed**

Example 107: synthesis of (17a'*R,*E)-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclopropane-1,9'-

[3,4](epirop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **107A**), (17a'*S,*E)-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclopropane-1,9'-

[3,4](epirop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **107B**).

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Compounds **107A** and **107B** were synthesized according to the procedures described in example **46** starting from intermediate **79c**.

5

Compound 107A:

LC/MS (method LC-C): Rt 2.73 min, MH⁺ 486
$$[\alpha]_{\text{D}}^{20}: +405.74^{\circ} (\text{c } 0.122, \text{DMF})$$

Chiral HPLC (method HPLC-B): Rt 6.89 min, chiral purity 100%

10

Compound 107B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.35 - 7.45 (m, 1 H) 7.23 (d, *J*=7.6 Hz, 1 H) 7.19 (d, *J*=8.2 Hz, 2 H) 7.09 - 7.14 (m, 1 H) 7.03 - 7.08 (m, 1 H) 6.83 - 6.90 (m, 2 H) 6.33 (ddd, *J*=15.4, 9.5, 5.7 Hz, 1 H) 5.68 - 5.77 (m, 2 H) 5.62 (d, *J*=7.6 Hz, 1 H) 5.49 (s, 1 H) 5.13 (d, *J*=13.6 Hz, 1 H) 4.88 (dd, *J*=11.0, 5.7 Hz, 1 H) 4.35 (t, *J*=10.2 Hz, 1 H) 4.16 (d, *J*=13.6 Hz, 1 H) 3.87 (d, *J*=13.6 Hz, 1 H) 1.51 (ddd, *J*=10.4, 7.3, 6.0 Hz, 1 H) 1.11 - 1.20 (m, 1 H) 0.87 - 0.96 (m, 1 H) 0.73 (ddd, *J*=9.5, 7.5, 5.0 Hz, 1 H)

LC/MS (method LC-C): Rt 2.73 min, MH⁺ 486

$$[\alpha]_{\text{D}}^{20}: -426.40^{\circ} \text{ (c 0.125, DMF)}$$

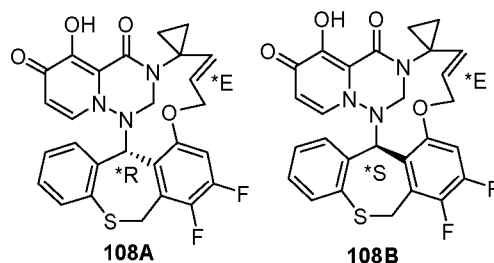
20

Chiral HPLC (method HPLC-B): Rt 9.05 min, chiral purity 100%

Example 108: synthesis of (17a**R*,**E*)-24',25'-difluoro-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclopropane-1,9']-

25 [3,4](epiprop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **108A**), (17a'*S,*E)-24',25'-difluoro-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclopropane-1,9']-[3,4](epiprop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **108B**).

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Compounds **108A** and **108B** were synthesized according to the procedures described in example **88** starting from intermediate **79c**.

5

Compound 108A:

LC/MS (method LC-C): Rt 2.96 min, MH⁺ 522

[α]_D²⁰: +391.8 ° (c 0.122, DMF)

Chiral HPLC (method HPLC-B): Rt 7.44 min, chiral purity 100%

10

Compound 108B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.46 (dd, *J*=11.7, 7.3 Hz, 1 H) 7.20 (d, *J*=7.6 Hz, 1 H) 7.12 - 7.17 (m, 1 H) 7.06 - 7.11 (m, 1 H) 6.83 - 6.95 (m, 2 H) 6.33 (ddd, *J*=15.4, 9.1, 6.0 Hz, 1 H) 5.86 (br d, *J*=15.4 Hz, 1 H) 5.58 - 5.67 (m, 2 H) 5.44 (s, 1 H) 5.09 (d, *J*=13.9 Hz, 1 H) 4.85 (dd, *J*=11.0, 6.0 Hz, 1 H) 4.39 (dd, *J*=10.9, 9.6 Hz, 1 H) 4.33 (d, *J*=13.9 Hz, 1 H) 4.10 (d, *J*=14.2 Hz, 1 H) 1.46 - 1.55 (m, 1 H) 1.13 - 1.21 (m, 1 H) 0.87 - 0.95 (m, 1 H) 0.76 (ddd, *J*=9.5, 7.6, 5.2 Hz, 1 H)

15

LC/MS (method LC-C): Rt 2.96 min, MH⁺ 522

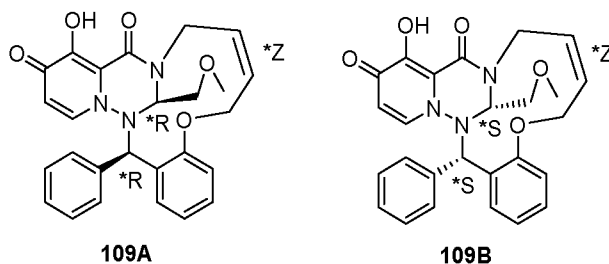
[α]_D²⁰: -410.85 ° (c 0.129, DMF)

20

Chiral HPLC (method HPLC-B): Rt 7.63 min, chiral purity 100%

Example 109: synthesis of (18^{*}R,19^{*}R,^{*}Z)-12-hydroxy-19-(methoxymethyl)-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **109A**), (18^{*}S,19^{*}S,^{*}Z)-12-hydroxy-19-(methoxymethyl)-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **109B**)

25



Compounds **109A** and **109B** were synthesized according to the procedures described in example **91** starting from intermediate **5a** and using methoxyacetaldehyde dimethyl acetal [CAS 10312-83-1] instead of acetaldehyde.

5 Compound 109A:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.08 (br d, $J=7.3$ Hz, 1 H) 7.38 - 7.49 (m, 1 H) 7.31 - 7.37 (m, 1 H) 7.02 - 7.29 (m, 7 H) 6.05 - 6.22 (m, 1 H) 5.82 - 6.03 (m, 1 H) 5.51 (d, $J=7.6$ Hz, 1 H) 5.29 (s, 1 H) 4.67 - 4.88 (m, 2 H) 4.45 (t, $J=6.1$ Hz, 1 H) 4.21 - 4.39 (m, 1 H) 3.45 - 3.55 (m, 2 H) 3.22 - 3.27 (m, 4 H)

10 LC/MS (method LC-C): Rt 2.61 min, MH^+ 460

$[\alpha]_{\text{D}}^{20}$: -602.82 ° (c 0.142, DMF)

Chiral HPLC (method HPLC-B): Rt 5.88 min, chiral purity 100%

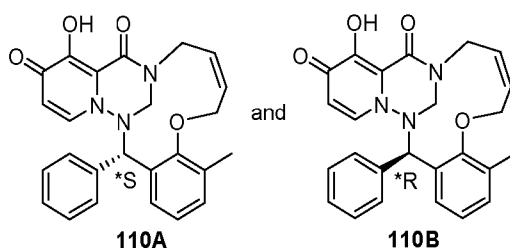
Compound 109B:

15 LC/MS (method LC-C): Rt 2.61 min, MH^+ 460

$[\alpha]_{\text{D}}^{20}$: +584.94 ° (c 0.166, DMF)

Chiral HPLC (method HPLC-B): Rt 4.62 min, chiral purity 100%

Example 110: synthesis of (18*S,Z)-12-hydroxy-4-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **110A**) and (18*R,Z)-12-hydroxy-4-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **110B**)



Compounds **110A** and **110B** were synthesized according to the procedures described in example **5** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-methylbenzene (synthesized as **74c** from 3-methyl-2-(2-propen-1-yloxy)-benzaldehyde [CAS 153034-23-2]).

Compound 110A:

LC/MS (method LC-C): Rt 2.65 min, MH^+ 430

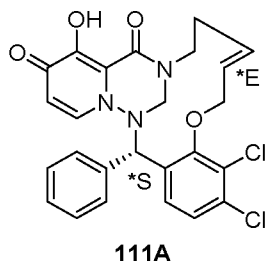
$[\alpha]_D^{20}$: +730.43° (c 0.138, DMF)

Chiral HPLC (method HPLC-B): Rt 4.93 min, chiral purity 99.38%

Compound 110B:

- 5 ^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.51 - 11.37 (m, 1 H) 7.89 (t, $J=4.7$ Hz, 1 H) 7.27 (d, $J=4.9$ Hz, 2 H) 6.90 - 7.23 (m, 6 H) 6.13 - 6.40 (m, 1 H) 5.67 - 5.92 (m, 1 H) 5.46 (d, $J=7.6$ Hz, 1 H) 5.30 (s, 1 H) 5.15 (d, $J=13.8$ Hz, 1 H) 4.83 (br dd, $J=13.8$, 4.8 Hz, 1 H) 4.74 (br dd, $J=10.6$, 5.9 Hz, 1 H) 4.33 (d, $J=13.6$ Hz, 1 H) 3.97 - 4.17 (m, 1 H) 3.21 (br dd, $J=13.9$, 7.5 Hz, 1 H) 2.21 (s, 3 H)
- 10 LC/MS (method LC-C): Rt 2.65 min, MH^+ 430
 $[\alpha]_D^{20}$: -724.07° (c 0.108, DMF)
 Chiral HPLC (method HPLC-B): Rt 3.26 min, chiral purity 100%

- Example 111: synthesis of (2*S,*E)-33,34-dichloro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **111A**)
- 15



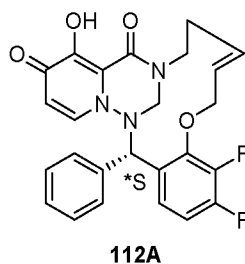
20

Compounds **111A** was synthesized according to the procedures described in example 10 starting from intermediate 2-(allyloxy)-3,4-dichloro-1-(chloro(phenyl)methyl)benzene (see example 103) .

Compound 111A:

- 25 ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.39 - 12.00 (m, 1 H) 8.10 (d, $J=8.7$ Hz, 1 H) 7.68 (d, $J=8.7$ Hz, 1 H) 7.11 - 7.26 (m, 4 H) 7.03 (br s, 2 H) 6.08 - 6.18 (m, 1 H) 6.07 (s, 1 H) 5.73 (ddd, $J=14.6$, 10.2, 4.2 Hz, 1 H) 5.38 (d, $J=7.6$ Hz, 1 H) 5.10 (d, $J=13.0$ Hz, 1 H) 4.76 (dd, $J=12.0$, 4.4 Hz, 1 H) 4.38 (d, $J=13.3$ Hz, 1 H) 4.14 (t, $J=11.3$ Hz, 1 H) 3.82 (br d, $J=13.2$ Hz, 1 H) 2.78 - 3.00 (m, 2 H) 2.27 (br d, $J=13.3$ Hz, 1 H)
- 30 LC/MS (method LC-C): Rt 3.12 min, MH^+ 498
 $[\alpha]_D^{20}$: -531.15° (c 0.122, DMF)

Example 112: synthesis of (2*S,E)-33,34-difluoro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **112A**)



5

Compounds **112A** was synthesized according to the procedures described in example **10** starting from intermediates **2a** and **74c**.

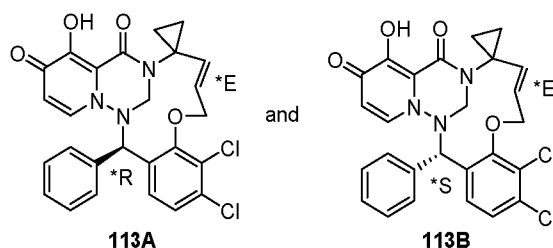
Compound 112A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.89 (br t, *J*=6.8 Hz, 1 H) 7.41 - 7.53 (m, 1 H) 6.81 - 7.39 (m, 6 H) 6.01 - 6.18 (m, 1 H) 5.92 (s, 1 H) 5.71 (ddd, *J*=15.1, 10.3, 4.6 Hz, 1 H) 5.38 (d, *J*=7.6 Hz, 1 H) 5.07 (d, *J*=12.9 Hz, 1 H) 4.78 (dd, *J*=11.8, 5.2 Hz, 1 H) 4.32 (d, *J*=13.2 Hz, 1 H) 4.11 (t, *J*=11.0 Hz, 1 H) 3.76 - 3.88 (m, 1 H) 2.78 - 2.99 (m, 2 H) 2.27 (br d, *J*=12.3 Hz, 1 H)

LC/MS (method LC-C): Rt 2.79 min, MH⁺ 466

[α]_D²⁰: -429.09 ° (c 0.11, DMF)

Example 113: synthesis of (18'*R,*E)-3',4'-dichloro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **113A**), (18'*S,*E)-3',4'-dichloro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **113B**)



25

Compounds **113A** and **113B** were synthesized according to the procedures described in example **79** starting from intermediate 2-(allyloxy)-3,4-dichloro-1-(chloro(phenyl)methyl) benzene (see example 103).

5 Compound 113A:

LC/MS (method LC-C): Rt 3.21 min, MH^+ 510

$[\alpha]_D^{20}$: +635.27 ° (c 0.207, DMF)

Chiral HPLC (method HPLC-B): Rt 6.39 min, chiral purity 100%

10 Compound 113B:

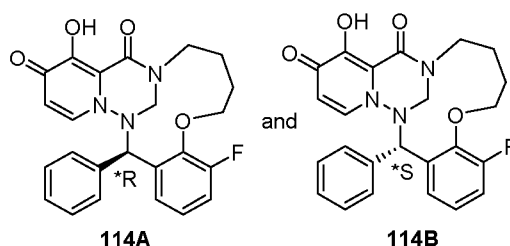
^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 8.07 (d, $J=8.5$ Hz, 1 H) 7.70 (d, $J=8.5$ Hz, 1 H) 6.97 - 7.44 (m, 6 H) 6.31 - 6.55 (m, 1 H) 5.83 (br d, $J=13.2$ Hz, 1 H) 5.50 (d, $J=7.6$ Hz, 1 H) 5.38 (s, 1 H) 5.15 (d, $J=13.9$ Hz, 1 H) 4.89 (br dd, $J=10.9$, 5.8 Hz, 1 H) 4.35 (br t, $J=10.2$ Hz, 1 H) 4.28 (d, $J=13.6$ Hz, 1 H) 1.55 (dt, $J=9.8$, 6.8 Hz, 1 H) 1.19 (dt, $J=9.5$, 6.4 Hz, 1 H) 0.85 - 0.97 (m, 1 H) 0.71 - 0.80 (m, 1 H)

LC/MS (method LC-C): Rt 3.21 min, MH^+ 510

$[\alpha]_D^{20}$: -663.91 ° (c 0.169, DMF)

Chiral HPLC (method HPLC-B): Rt 7.11 min, chiral purity 100%

20 Example 114: (18*R)-4-fluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **114A**) and (18*S)-4-fluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **114B**)



Compounds **114A** and **114B** were synthesized according to the procedures described in example **8** starting from intermediates **61da** and **61db**.

30 Compound 114A:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 10.26 - 12.37 (m, 1 H) 7.72 - 7.83 (m, 1 H) 7.19 - 7.35 (m, 4 H) 7.13 - 7.19 (m, 3 H) 7.10 (d, $J=7.9$ Hz, 1 H) 5.77 (s, 1 H) 5.44 (d, $J=7.9$

Hz, 1 H) 5.01 (d, $J=13.6$ Hz, 1 H) 4.38 (br d, $J=12.3$ Hz, 1 H) 4.30 (d, $J=13.6$ Hz, 1 H) 3.92 - 4.12 (m, 2 H) 2.63 (br d, $J=13.9$ Hz, 1 H) 1.74 - 1.97 (m, 2 H) 1.49 - 1.66 (m, 1 H) 0.91 - 1.08 (m, 1 H)

LC/MS (method LC-C): Rt 2.64 min, MH^+ 436

5 $[\alpha]_D^{20}$: -336.88 ° (c 0.141, DMF)

Chiral HPLC (method HPLC-B): Rt 6.03 min, chiral purity 100%

Compound 114B:

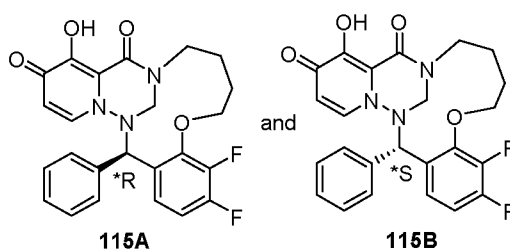
LC/MS (method LC-C): Rt 2.64 min, MH^+ 436

10 $[\alpha]_D^{20}$: +331.55 ° (c 0.168, DMF)

Chiral HPLC (method HPLC-B): Rt 4.71 min, chiral purity 100%

Example 115: (18*R)-3,4-difluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

15 (Compound 115A) and (18*S)-3,4-difluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound 115B)



20

Compounds 115A and 115B were synthesized according to the procedures described in example 8 starting from intermediates 74ea and 74eb.

Compound 115A:

25 LC/MS (method LC-C): Rt 2.74 min, MH^+ 454

$[\alpha]_D^{20}$: +320.41 ° (c 0.098, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 115B:

30 ^1H NMR (500 MHz, DMSO- d_6) δ ppm 10.42 - 12.05 (m, 1 H) 7.79 (br t, $J=6.8$ Hz, 1 H) 7.30 - 7.42 (m, 1 H) 7.00 - 7.28 (m, 6 H) 5.70 (s, 1 H) 5.44 (d, $J=7.6$ Hz, 1 H) 5.00 (d, $J=13.9$ Hz, 1 H) 4.44 (br d, $J=12.3$ Hz, 1 H) 4.32 (d, $J=13.9$ Hz, 1 H) 3.95 - 4.16

(m, 2 H) 2.62 (br d, $J=13.9$ Hz, 1 H) 1.75 - 1.97 (m, 2 H) 1.55 - 1.72 (m, 1 H) 0.94 - 1.11 (m, 1 H)

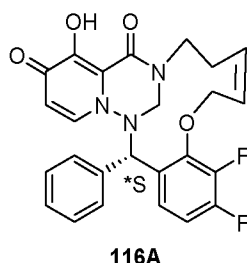
LC/MS (method LC-C): Rt 2.74 min, MH^+ 454

$[\alpha]_D^{20}$: -308.21 ° (c 0.207, DMF)

5 Chiral HPLC (method HPLC-A and B): **No separation observed**

Example 116: synthesis of (2*S,Z)-33,34-difluoro-15-hydroxy-2-phenyl-12,13,14,16-tetrahydro-11H-4-oxa-1(1,3)-pyrido[2,1-f][1,2,4]triazina-3(1,2)-benzenacyclononaphan-6-ene-14,16-dione (enantiomer **116A**)

10



Compounds **116A** was synthesized according to the procedures described in example 10 starting from intermediate **74c**.

15

Compound 116A:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 10.71 - 12.27 (m, 1 H) 7.84 (br t, $J=6.8$ Hz, 1 H) 7.30 - 7.40 (m, 1 H) 7.23 (d, $J=7.6$ Hz, 1 H) 6.80 - 7.18 (m, 5 H) 5.96 - 6.05 (m, 1 H) 5.88 - 5.95 (m, 1 H) 5.69 (s, 1 H) 5.37 (d, $J=7.9$ Hz, 1 H) 4.97 (d, $J=13.2$ Hz, 1 H) 4.70 (dd, $J=11.3, 6.0$ Hz, 1 H) 4.43 (br t, $J=10.2$ Hz, 1 H) 4.27 - 4.35 (m, 2 H) 2.79 (br d, $J=13.9$ Hz, 1 H) 2.48 - 2.54 (m, 1 H) 2.12 (br d, $J=15.8$ Hz, 1 H)

20

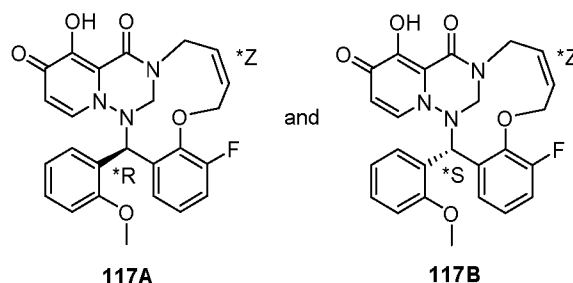
LC/MS (method LC-C): Rt 2.81 min, MH^+ 466

$[\alpha]_D^{20}$: -316.03 ° (c 0.156, DMF)

Example 117: synthesis of (18*R,*Z)-4-fluoro-12-hydroxy-18-(2-methoxyphenyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **117A**) and ((18*S,*Z)-4-fluoro-12-hydroxy-18-(2-methoxyphenyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **117B**)

30

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Compounds **117A** and **117B** were synthesized according to the procedures described in example **5** starting from intermediate 2-(allyloxy)-1-(chloro(2-methoxyphenyl)methyl)-3-fluorobenzene (synthesized as **23a** from 2-bromoanisole [CAS 578-57-4] and 3-fluoro-2-(2-propen-1-yloxy)benzaldehyde [CAS 1006304-54-4]).

Compound 117A:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.34 - 11.38 (m, 1 H) 7.92 (br d, *J*=7.1 Hz, 1 H) 7.29 - 7.47 (m, 2 H) 7.04 - 7.22 (m, 3 H) 6.70 - 6.88 (m, 2 H) 6.09 - 6.28 (m, 2 H) 5.85 - 6.08 (m, 1 H) 5.47 (d, *J*=7.6 Hz, 1 H) 5.08 (d, *J*=13.6 Hz, 1 H) 4.87 (br dd, *J*=13.8, 4.0 Hz, 1 H) 4.62 - 4.79 (m, 1 H) 4.11 - 4.38 (m, 2 H) 3.53 (s, 3 H) 3.25 (br dd, *J*=13.7, 8.4 Hz, 1 H)

LC/MS (method LC-C): Rt 2.59 min, MH⁺ 464

[α]_D²⁰: -653.6 ° (c 0.222, DMF)

Chiral HPLC (method HPLC-B): Rt 4.48 min, chiral purity 100%

Compound 117B:

LC/MS (method LC-C): Rt 2.59 min, MH⁺ 464

[α]_D²⁰: +674.02° (c 0.204, DMF)

Chiral HPLC (method HPLC-B): Rt 4.21 min, chiral purity 100%

Example 118: synthesis of (1a*R,11b*S,20a*S)-17-hydroxy-1a,2,6,11b,17,17a,20,20a-octahydro-1H-5,4-(epiprop[1]en[1]yl[3]ylidene)-12,19-

methanobenzo[6,7]thiepino[4,5-c]cyclopropa[k]pyrido[1,2-

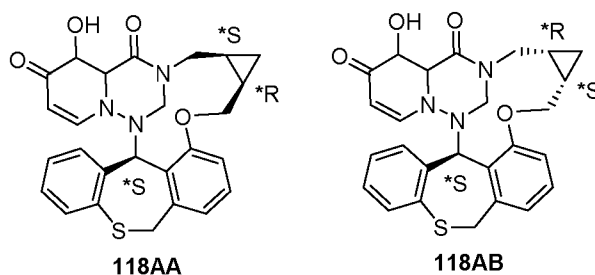
f][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **118AA**),

(1a*S,11b*S,20a*R)-17-hydroxy-1a,2,6,11b,17,17a,20,20a-octahydro-1H-5,4-

(epiprop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-

c]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound

118AB)



Compounds **118AA** and **118AB** were synthesized according to the procedures described in example **87** starting from intermediate cis-((1RS,2RS)-2-(((tert-butyl)diphenylsilyl)oxy)methyl)cyclopropyl)methanamine.

Compound **118AA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.36 - 11.81 (m, 1 H) 7.37 - 7.43 (m, 1 H) 7.33 (t, *J*=8.0 Hz, 2 H) 7.04 - 7.20 (m, 3 H) 6.76 - 6.84 (m, 1 H) 6.61 (d, *J*=7.6 Hz, 1 H) 6.16 (s, 1 H) 5.75 (d, *J*=13.6 Hz, 1 H) 5.62 (d, *J*=7.6 Hz, 1 H) 5.06 (br dd, *J*=13.2, 4.7 Hz, 1 H) 4.95 (d, *J*=12.9 Hz, 1 H) 4.70 (d, *J*=13.2 Hz, 1 H) 3.82 - 3.95 (m, 2 H) 3.79 (d, *J*=13.6 Hz, 1 H) 3.56 - 3.67 (m, 1 H) 1.29 - 1.37 (m, 1 H) 0.99 - 1.07 (m, 1 H) 0.88 (td, *J*=8.5, 4.1 Hz, 1 H) 0.58 (q, *J*=4.7 Hz, 1 H)

LC/MS (method LC-C): Rt 2.74 min, MH⁺ 474

[α]_D²⁰: -211.69° (c 0.154, DMF)

Chiral HPLC (method HPLC-B): Rt 8.50 min, chiral purity 100%

Compound **118AB**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.77 - 12.15 (m, 1 H) 7.38 (t, *J*=7.9 Hz, 1 H) 7.28 (d, *J*=7.9 Hz, 1 H) 7.11 - 7.17 (m, 2 H) 7.08 (br d, *J*=3.5 Hz, 2 H) 6.82 - 6.89 (m, 1 H) 6.70 (d, *J*=7.6 Hz, 1 H) 6.46 (s, 1 H) 5.70 (d, *J*=14.2 Hz, 1 H) 5.61 (d, *J*=7.6 Hz, 1 H) 4.94 - 5.05 (m, 2 H) 4.03 - 4.14 (m, 2 H) 3.77 (d, *J*=13.9 Hz, 1 H) 3.35 - 3.41 (m, 1 H) 2.66 - 2.75 (m, 1 H) 2.06 - 2.19 (m, 1 H) 1.50 - 1.65 (m, 1 H) 0.85 - 0.94 (m, 1 H) 0.16 (q, *J*=5.4 Hz, 1 H)

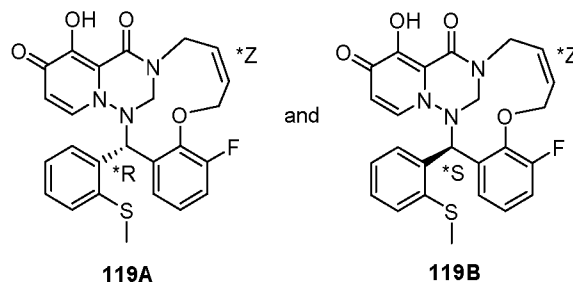
LC/MS (method LC-C): Rt 2.74 min, MH⁺ 474

[α]_D²⁰: -209.03° (c 0.144, DMF)

Chiral HPLC (method HPLC-B): Rt 7.63 min, chiral purity 100%

Example 119: synthesis of (18*R,*Z)-4-fluoro-12-hydroxy-18-(2-(methylthio)phenyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **119A**) and (18*S,*Z)-4-fluoro-12-hydroxy-18-(2-(methylthio)phenyl)-6,9-dihydro-18H-10,17-

methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(compound **119B**)



5

Compounds **119A** and **119B** were synthesized according to the procedures described in example **5** starting from intermediate (2-((2-(allyloxy)-3-fluorophenyl)chloromethyl)phenyl)(methyl)sulfane (synthesized as **23a** from 1-bromo-2-methylthiobenzene [CAS 19614-16-5] and 3-fluoro-2-(2-propen-1-yloxy)benzaldehyde [CAS 1106304-54-4]).

Compound 119A:

$$[\alpha]_{\text{D}}^{20}: +670.86^{\circ} (\text{c } 0.175, \text{DMF})$$

Chiral HPLC (method HPLC-A): Rt 7.54 min, chiral purity 98.93%

Compound 119B:

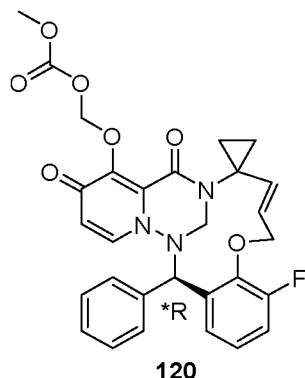
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.72 - 12.25 (m, 1 H) 7.92 (br d, *J*=7.6 Hz, 1 H) 7.49 (d, *J*=7.3 Hz, 1 H) 7.40 (td, *J*=8.0, 5.5 Hz, 1 H) 7.26 - 7.36 (m, 2 H) 7.17 - 7.23 (m, 1 H) 7.09 - 7.16 (m, 2 H) 6.23 - 6.47 (m, 2 H) 5.82 - 6.11 (m, 1 H) 5.46 (d, *J*=7.9 Hz, 1 H) 5.13 (d, *J*=13.9 Hz, 1 H) 4.86 (br dd, *J*=14.2, 4.7 Hz, 1 H) 4.73 - 4.82 (m, 1 H) 4.13 - 4.33 (m, 2 H) 3.20 - 3.25 (m, 1 H) 2.28 (s, 3 H)

$$[\alpha]_{\text{D}}^{20}: -701.36^{\circ} \text{ (c 0.22, DMF)}$$

Chiral HPLC (method HPLC-A): Rt 5.95 min, chiral purity 100%

Example 120: synthesis of (((18'R,E)-4'-fluoro-11',13'-dioxo-18'-phenyl-11',13'-dihydro-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin]-12'-yl)oxy)methyl methyl carbonate (Compound **120**)

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Compounds **120** was synthesized according to the procedure described in example **62** starting from compound **95B** and using 1,8diazabicyclo[5.4.0]undec-7-ene (DBU) and CH₃CN.

5

Compound 120:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.90 (d, *J*=7.7 Hz, 1 H) 7.32 - 7.47 (m, 2 H) 7.06 - 7.31 (m, 6 H) 6.25 - 6.46 (m, 1 H) 5.82 - 5.99 (m, 1 H) 5.74 - 5.80 (m, 1 H) 5.71 (d, *J*=7.8 Hz, 1 H) 5.53 (d, *J*=6.6 Hz, 1 H) 5.33 (s, 1 H) 5.12 (d, *J*=13.8 Hz, 1 H) 4.83 (br dd, *J*=10.9, 6.4 Hz, 1 H) 4.11 - 4.26 (m, 2 H) 3.78 (s, 3 H) 1.26 - 1.37 (m, 1 H) 1.16 (dt, *J*=9.6, 6.5 Hz, 1 H) 0.78 - 0.91 (m, 1 H) 0.68 - 0.77 (m, 1 H)

10

LC/MS (method LC-B): Rt 2.57 min, MH⁺ 548

[α]_D²⁰: -480.51 ° (c 0.195, DMF)

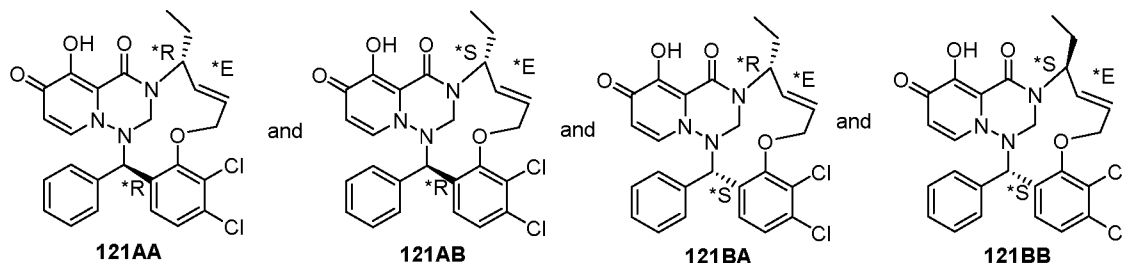
Chiral HPLC (method HPLC-B): Rt 7.85 min, chiral purity 100%

15

Example 121: synthesis of (9*R,18*R,*E)-3,4-dichloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **121AA**) and (9*S,18*R,*E)-3,4-dichloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **121AB**) and (9*R,18*S,*E)-3,4-dichloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **121BA**) and (9*S,18*S,*E)-3,4-dichloro-9-ethyl-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **121BB**)

20

25



Compounds **121AA**, **121AB**, **121BA** and **121BB** were synthesized according to the procedures described in example **39** starting from intermediate 2-(allyloxy)-3,4-dichloro-1-(chloro(phenyl)methyl)benzene (see example 103).

Compound 121AA:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.13 (d, $J=8.5$ Hz, 1 H) 7.70 (d, $J=8.8$ Hz, 1 H) 6.99 - 7.39 (m, 6 H) 6.41 (ddd, $J=15.4, 10.4, 5.0$ Hz, 1 H) 5.66 (br dd, $J=15.6, 6.5$ Hz, 1 H) 5.48 (d, $J=7.6$ Hz, 1 H) 5.24 (s, 1 H) 5.18 (q, $J=7.6$ Hz, 1 H) 5.07 (d, $J=13.6$ Hz, 1 H) 4.89 (br dd, $J=11.7, 5.0$ Hz, 1 H) 4.29 (d, $J=13.6$ Hz, 1 H) 4.12 (br t, $J=11.0$ Hz, 1 H) 1.41 - 1.66 (m, 2 H) 0.84 (br t, $J=7.3$ Hz, 3 H)

LC/MS (method LC-C): Rt 3.34 min, MH^+ 512

$[\alpha]_{\text{D}}^{20}$: -564.94 $^\circ$ (c 0.154, DMF)

Chiral HPLC (method HPLC-B): Rt 7.11 min, chiral purity 100%

Compound 121AB:

LC/MS (method LC-C): Rt 3.37 min, MH^+ 512

$[\alpha]_{\text{D}}^{20}$: +755.34 $^\circ$ (c 0.103, DMF)

Chiral HPLC (method HPLC-B): Rt 4.80 min, chiral purity 100%

Compound 121BA:

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.09 (d, $J=8.5$ Hz, 1 H) 7.63 (d, $J=8.8$ Hz, 1 H) 7.26 (br d, $J=7.6$ Hz, 1 H) 6.82 - 7.20 (m, 5 H) 6.28 - 6.57 (m, 1 H) 5.67 - 5.97 (m, 1 H) 5.42 (d, $J=7.6$ Hz, 1 H) 5.36 (s, 1 H) 5.16 (d, $J=13.9$ Hz, 1 H) 4.72 - 4.88 (m, 1 H) 4.55 - 4.68 (m, 1 H) 4.22 (br d, $J=14.2$ Hz, 1 H) 3.35 - 3.43 (m, 1 H) 2.20 - 2.28 (m, 1 H) 2.03 - 2.15 (m, 1 H) 0.80 (t, $J=7.4$ Hz, 3 H)

LC/MS (method LC-C): Rt 3.37 min, MH^+ 512

$[\alpha]_{\text{D}}^{20}$: -732.23 $^\circ$ (c 0.121, DMF)

Chiral HPLC (method HPLC-B): Rt 4.83 min, chiral purity 100%

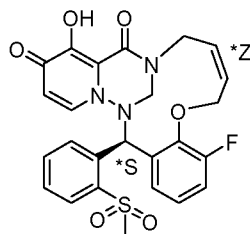
Compound 121BB:

LC/MS (method LC-C): Rt 3.34 min, MH^+ 512

$[\alpha]_D^{20}$: +606.32 ° (c 0.190, DMF)

Chiral HPLC (method HPLC-B): Rt 5.55 min, chiral purity 100%

Example 122: synthesis of (18*S,*Z)-4-fluoro-12-hydroxy-18-(2-(methylsulfonyl)phenyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **122**)



122

Compound **122** was synthesized according to the procedures described in example **82** starting from the O-benzyl protected 119A.

Compound 122:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 11.26 - 11.67 (m, 1 H) 8.11 (d, $J=7.6$ Hz, 1 H) 8.02 (br d, $J=7.6$ Hz, 1 H) 7.84 (dd, $J=8.2, 1.3$ Hz, 1 H) 7.62 - 7.73 (m, 1 H) 7.50 - 7.58 (m, 1 H) 7.42 - 7.48 (m, 1 H) 7.34 - 7.41 (m, 1 H) 7.06 (br d, $J=7.3$ Hz, 1 H) 6.89 (s, 1 H) 6.20 - 6.47 (m, 1 H) 5.73 - 6.01 (m, 1 H) 5.43 (d, $J=7.9$ Hz, 1 H) 5.12 (d, $J=13.9$ Hz, 1 H) 4.83 - 4.94 (m, 1 H) 4.79 (dd, $J=14.0, 4.3$ Hz, 1 H) 4.18 - 4.37 (m, 2 H) 3.25 (s, 3 H) 3.18 (dd, $J=14.2, 7.6$ Hz, 1 H)

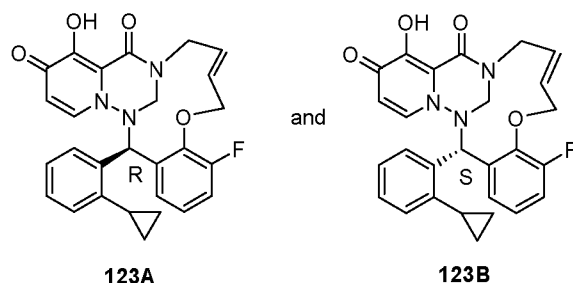
LC/MS (method LC-C): Rt 2.31 min, MH^+ 512

$[\alpha]_D^{20}$: -570.59 ° (c 0.102, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Example 123: synthesis (18R,E)-18-(2-cyclopropylphenyl)-4-fluoro-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **123A**) and (18S,E)-18-(2-cyclopropylphenyl)-4-fluoro-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **123B**)

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Compounds **123A** and **123B** were synthesized according to the procedures described in example **5** starting from intermediate 2-(allyloxy)-1-(chloro(2-cyclopropylphenyl)methyl)-3-fluorobenzene (synthesized as **23a** from 1-bromo-2-cyclopropylbenzene [CAS 57807-28-0] and 3-fluoro-2-(2-propen-1-yloxy)benzaldehyde [CAS 1106304-54-4].

Compound 123A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 (br d, *J*=7.9 Hz, 1 H) 7.57 - 7.67 (m, 1 H) 7.40 (td, *J*=8.0, 5.4 Hz, 1 H) 7.29 - 7.36 (m, 1 H) 7.26 (br d, *J*=7.6 Hz, 1 H) 7.03 - 7.14 (m, 2 H) 6.77 - 6.87 (m, 1 H) 6.10 - 6.24 (m, 1 H) 6.06 (br s, 1 H) 5.84 - 5.98 (m, 1 H) 5.51 (d, *J*=7.9 Hz, 1 H) 5.18 (d, *J*=13.9 Hz, 1 H) 4.76 - 4.88 (m, 2 H) 4.37 (d, *J*=13.9 Hz, 1 H) 4.24 (br s, 1 H) 3.25 (br dd, *J*=13.9, 7.9 Hz, 1 H) 2.01 - 2.10 (m, 1 H) 0.85 - 0.99 (m, 2 H) 0.76 - 0.84 (m, 1 H) 0.00 - 0.05 (m, 1 H)

LC/MS (method LC-C): Rt 2.78 min, MH⁺ 474

[α]_D²⁰: -700.56 ° (c 0.177, DMF)

Chiral HPLC (method HPLC-A): Rt 5.42 min, chiral purity 100%

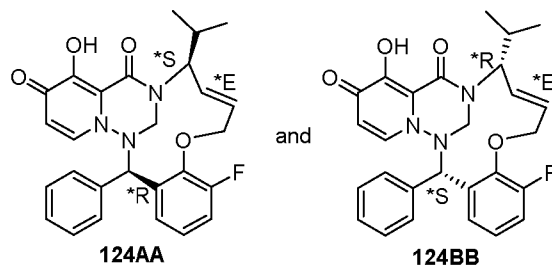
Compound 123B:

LC/MS (method LC-C): Rt 2.78 min, MH⁺ 474

[α]_D²⁰: +721.21 ° (c 0.165, DMF)

Chiral HPLC (method HPLC-A): Rt 5.90 min, chiral purity 100%

Example 124: synthesis of (9*S,18*R,*E)-4-fluoro-12-hydroxy-9-isopropyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **124AA**) and (9*R,18*S,*E)-4-fluoro-12-hydroxy-9-isopropyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **124BB**)



Compounds **124AA** and **124BB** were synthesized according to the procedures described in example **39** starting from intermediates 5-hydroxy-3-(4-methylpent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized as **39e** from 4-methylpent-1-en-3-amine [CAS 127209-34-1] and 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene **61b**).

Compound 124AA:

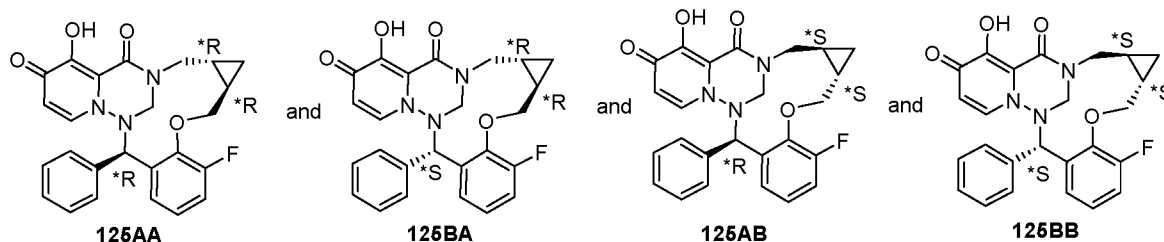
- LC/MS (method LC-C): Rt 3.03 min, MH^+ 476
 $[\alpha]_D^{20}$: +522.41 ° (c 0.116, DMF)
 Chiral HPLC (method HPLC-B): Rt 5.90 min, chiral purity 100%

Compound 124BB:

- ^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.93 (br d, $J=7.6$ Hz, 1 H) 7.39 - 7.45 (m, 1 H) 7.33 - 7.39 (m, 1 H) 7.02 - 7.31 (m, 6 H) 6.38 (ddd, $J=15.4, 10.1, 5.4$ Hz, 1 H) 5.60 (br dd, $J=15.8, 6.9$ Hz, 1 H) 5.48 (d, $J=7.6$ Hz, 1 H) 5.22 (s, 1 H) 5.10 (br d, $J=13.6$ Hz, 1 H) 4.87 (br dd, $J=11.3, 6.0$ Hz, 2 H) 4.24 (br d, $J=13.6$ Hz, 1 H) 4.01 (br t, $J=10.9$ Hz, 1 H) 1.60 - 1.79 (m, 1 H) 0.85 (br d, $J=4.4$ Hz, 6 H)
 LC/MS (method LC-C): Rt 3.03 min, MH^+ 476
 $[\alpha]_D^{20}$: -638.98 ° (c 0.118, DMF)
 Chiral HPLC (method HPLC-B): Rt 5.61 min, chiral purity 100%

Example 125: synthesis of (1a^{*}R,8^{*}R,17a^{*}R)-4-fluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **125AA**), (1a^{*}R,8^{*}S,17a^{*}R)-4-fluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **125AB**), (1a^{*}S,8^{*}R,17a^{*}S)-4-fluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **125BA**) and (1a^{*}S,8^{*}S,17a^{*}S)-4-fluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-

methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **125BB**)



5

Compounds **125AA**, **125AB**, **125BA** and **125BB** were synthesized according to the procedures described in example **80** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluorobenzene **61b**.

10 **Compound 125AA:**

^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.99 (br d, $J=7.6$ Hz, 1 H) 7.21 - 7.40 (m, 3 H) 7.12 (br s, 5 H) 5.98 (s, 1 H) 5.43 (d, $J=7.6$ Hz, 1 H) 5.09 (br d, $J=13.6$ Hz, 1 H) 4.66 (br dd, $J=12.1$, 2.7 Hz, 1 H) 4.32 (br d, $J=13.6$ Hz, 2 H) 3.29 - 3.37 (m, 1 H) 2.11 (br dd, $J=13.6$, 11.7 Hz, 1 H) 1.34 (br s, 1 H) 0.93 - 1.10 (m, 1 H) 0.48 (dt, $J=8.8$, 4.4 Hz, 1 H) 0.31 (dt, $J=8.9$, 4.5 Hz, 1 H)

LC/MS (method LC-C): Rt 2.69 min, MH^+ 448

$[\alpha]_{\text{D}}^{20}$: -483.78 $^\circ$ (c 0.148, DMF)

Chiral HPLC (method HPLC-B): Rt 4.33 min, chiral purity 100%

20 **Compound 125BA:**

LC/MS (method LC-C): Rt 2.71 min, MH^+ 448

$[\alpha]_{\text{D}}^{20}$: +282.00 $^\circ$ (c 0.100, DMF)

Chiral HPLC (method HPLC-B): Rt 4.71 min, chiral purity 100%

25 **Compound 125BB:**

LC/MS (method LC-C): Rt 2.69 min, MH^+ 448

$[\alpha]_{\text{D}}^{20}$: +458.06 $^\circ$ (c 0.155, DMF)

Chiral HPLC (method HPLC-B): Rt 4.33 min, chiral purity 100%

30 **Compound 125AB:**

^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.89 (d, $J=7.6$ Hz, 1 H) 7.30 - 7.37 (m, 1 H) 7.17 - 7.30 (m, 7 H) 5.98 (s, 1 H) 5.50 (d, $J=7.6$ Hz, 1 H) 5.10 (d, $J=13.6$ Hz, 1 H) 4.84 (dd, $J=12.9$, 4.1 Hz, 1 H) 4.56 (d, $J=13.6$ Hz, 1 H) 3.58 (br dd, $J=14.5$, 10.7 Hz, 1 H)

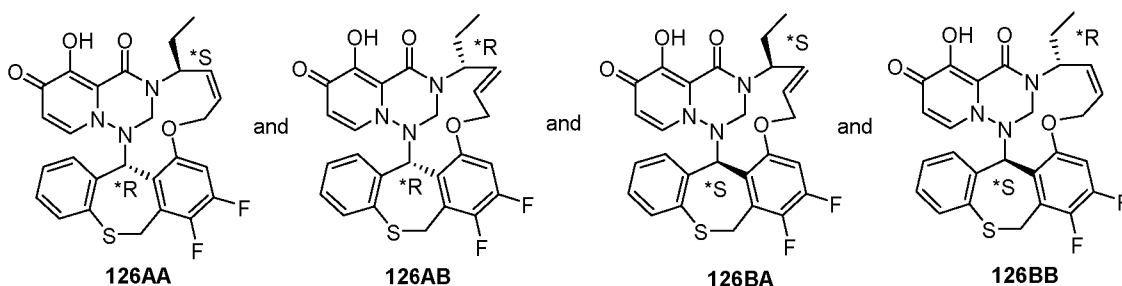
3.12 - 3.25 (m, 2 H) 1.34 - 1.47 (m, 1 H) 0.88 (td, $J=9.2, 4.9$ Hz, 1 H) 0.70 (dt, $J=8.7, 4.5$ Hz, 1 H) 0.50 - 0.59 (m, 1 H)

LC/MS (method LC-C): Rt 2.71 min, MH^+ 448

$[\alpha]_D^{20}$: -299.14 ° (c 0.116, DMF)

5 Chiral HPLC (method HPLC-B): Rt 5.55 min, chiral purity 100%

Example 126: synthesis of (13*S,21a*R,Z)-13-ethyl-24,25-difluoro-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **126AA**), (9*R,17a*R,E)-9-ethyl-24,25-difluoro-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi-prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **126AB**), (9*S,17a*S,E)-9-ethyl-24,25-difluoro-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi-prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **126BA**), (13*R,21a*S,Z)-13-ethyl-24,25-difluoro-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **126BB**).



Compounds **126AA**, **126AB**, **126BA** and **126BB** were synthesized according to the procedures described in example **88** starting from intermediate **39e**.

Compound 126AA:

LC/MS (method LC-C): Rt 3.17 min, MH^+ 524

$[\alpha]_D^{20}$: +115.09 ° (c 0.212, DMF)

Chiral HPLC (method HPLC-B): Rt 4.29 min, chiral purity 100%

Compound 126AB:

LC/MS (method LC-C): Rt 3.08 min, MH^+ 524

$[\alpha]_D^{20}$: +423.19 ° (c 0.138, DMF)

Chiral HPLC (method HPLC-B): Rt 5.57 min, chiral purity 100%

Compound 126BA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.06 - 11.91 (m, 1 H) 7.43 (br dd, *J*=11.5, 7.4 Hz, 1 H) 7.26 (d, *J*=7.6 Hz, 1 H) 7.11 - 7.18 (m, 1 H) 7.04 - 7.11 (m, 1 H) 6.86 - 6.92 (m, 1 H) 6.79 - 6.85 (m, 1 H) 6.33 (ddd, *J*=15.4, 9.8, 5.7 Hz, 1 H) 5.58 - 5.74 (m, 3 H) 5.27 (s, 1 H) 5.16 (q, *J*=7.6 Hz, 1 H) 5.02 (d, *J*=13.9 Hz, 1 H) 4.85 (br dd, *J*=11.5, 5.5 Hz, 1 H) 4.43 (d, *J*=13.6 Hz, 1 H) 4.31 (br t, *J*=10.7 Hz, 1 H) 4.12 (br d, *J*=14.2 Hz, 1 H) 1.42 - 1.69 (m, 2 H) 0.83 (br t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.08 min, MH⁺ 524

[α]_D²⁰: -436.7 ° (c 0.109, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 126BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.86 - 12.40 (m, 1 H) 7.36 (dd, *J*=11.8, 6.8 Hz, 1 H) 7.07 - 7.25 (m, 3 H) 6.78 - 6.92 (m, 1 H) 6.53 (d, *J*=7.6 Hz, 1 H) 6.48 (t, *J*=9.9 Hz, 1 H) 6.22 (dt, *J*=10.6, 7.0 Hz, 1 H) 5.98 (s, 1 H) 5.54 - 5.68 (m, 2 H) 5.17 (d, *J*=13.2 Hz, 1 H) 4.79 (dd, *J*=10.2, 6.8 Hz, 1 H) 4.49 (d, *J*=13.6 Hz, 1 H) 4.43 (br t, *J*=8.8 Hz, 1 H) 4.04 (d, *J*=14.2 Hz, 1 H) 3.84 (q, *J*=7.6 Hz, 1 H) 1.89 (br dd, *J*=13.9, 6.9 Hz, 1 H)

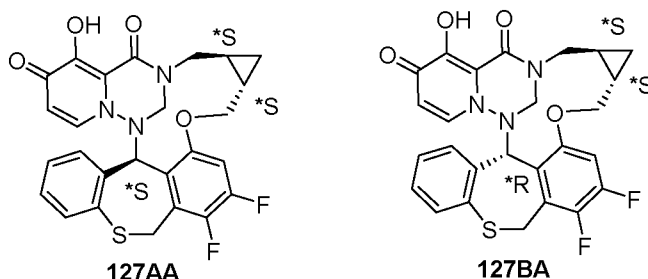
1.72 - 1.83 (m, 1 H) 0.83 (t, *J*=7.4 Hz, 3 H)

LC/MS (method LC-C): Rt 3.19 min, MH⁺ 524

[α]_D²⁰: -118.70 ° (c 0.123, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Example 127: synthesis of (1a*S,11b*S,20a*S)-22,23-difluoro-17-hydroxy-1a,2,6,11b,20,20a-hexahydro-1H-5,4-(epiprop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-c]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **127AA**), (1a*S,11b*R,20a*S)-22,23-difluoro-17-hydroxy-1a,2,6,11b,20,20a-hexahydro-1H-5,4-(epiprop[1]en[1]yl[3]ylidene)-12,19-methanobenzo[6,7]thiepino[4,5-c]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-16,18-dione (Compound **127BA**)



Compounds **127AA** and **127BA** were synthesized according to the procedures described in example **87** starting from intermediate **88n**.

5 Compound 127AA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.78 - 12.30 (m, 1 H) 7.28 (br dd, *J*=12.3, 7.0 Hz, 1 H) 7.06 - 7.21 (m, 3 H) 6.88 (t, *J*=7.3 Hz, 1 H) 6.76 (d, *J*=7.6 Hz, 1 H) 6.01 (s, 1 H) 5.56 - 5.70 (m, 2 H) 5.04 (br d, *J*=13.7 Hz, 1 H) 4.82 (dd, *J*=12.7, 5.0 Hz, 1 H) 4.65 (d, *J*=13.7 Hz, 1 H) 4.10 (d, *J*=14.1 Hz, 1 H) 3.46 - 3.57 (m, 2 H) 3.12 (br dd, *J*=14.3, 5.1 Hz, 1 H) 1.28 - 1.41 (m, 1 H) 1.00 (td, *J*=9.1, 4.7 Hz, 1 H) 0.79 (dt, *J*=8.5, 4.4 Hz, 1 H) 0.66 (dt, *J*=8.4, 4.4 Hz, 1 H)

LC/MS (method LC-C): Rt 2.92 min, MH⁺ 510

[α]_D²⁰: -152.03 ° (c 0.148, DMF)

Chiral HPLC (method HPLC-B): Rt 8.81 min, chiral purity 97.46%

Compound 127BA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.18 - 11.92 (m, 1 H) 7.66 (br dd, *J*=12.5, 7.3 Hz, 1 H) 7.39 (d, *J*=7.7 Hz, 1 H) 7.04 - 7.20 (m, 2 H) 6.88 (t, *J*=7.2 Hz, 1 H) 6.77 (br d, *J*=7.6 Hz, 1 H) 6.12 (s, 1 H) 5.81 (br d, *J*=15.0 Hz, 1 H) 5.62 (d, *J*=7.6 Hz, 1 H) 5.10 (br d, *J*=13.7 Hz, 1 H) 4.89 (br dd, *J*=12.2, 2.6 Hz, 1 H) 4.49 (br d, *J*=13.6 Hz, 1 H) 4.31 (br d, *J*=12.5 Hz, 1 H) 4.10 (br d, *J*=14.1 Hz, 1 H) 3.36 - 3.42 (m, 1 H) 2.02 - 2.15 (m, 1 H) 1.13 - 1.40 (m, 2 H) 0.63 (dt, *J*=8.8, 4.6 Hz, 1 H) 0.37 - 0.52 (m, 1 H)

LC/MS (method LC-C): Rt 2.89 min, MH⁺ 510

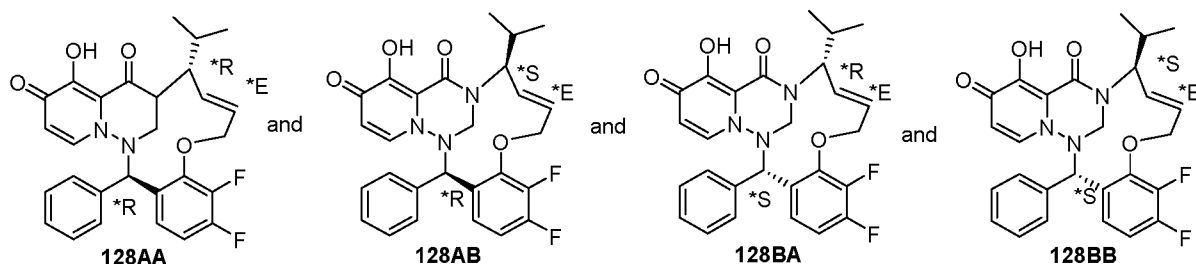
[α]_D²⁰: -280.13° (c 0.156, DMF)

Chiral HPLC (method HPLC-B): Rt 6.54 min, chiral purity 97.58%

Example 128: synthesis of (9*R,18*R,*E)-3,4-difluoro-12-hydroxy-9-isopropyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **128AA**) (9*S,18*R,*E)-3,4-difluoro-12-hydroxy-9-isopropyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **128AB**) and (9*R,18*S,*E)-3,4-difluoro-12-hydroxy-9-isopropyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **128BA**) and
 (9*S,18*S,*E)-9-ethyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-
 methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
 (Compound **128BB**)

5



Compounds **128AA**, **128AB**, **128BA** and **128BB** were synthesized according to the
 procedures described in example **39** starting from intermediates 5-hydroxy-3-(4-
 methylpent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (see
 example 124) and 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene **74c**.

Compound **128AA**:

LC/MS (method LC-C): Rt 3.12 min, MH⁺ 494

[α]_D²⁰: +564.63 ° (c 0.147, DMF)

Chiral HPLC (method HPLC-B): Rt 4.18 min, chiral purity 100%

Compound **128AB**:

LC/MS (method LC-C): Rt 3.29 min, MH⁺ 494

[α]_D²⁰: +306.67 ° (c 0.135, DMF)

Chiral HPLC (method HPLC-A): Rt 4.93 min, chiral purity 100%

Compound **128BA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.01 - 11.61 (m, 1 H) 7.52 (br d, *J*=7.6 Hz, 1
 H) 7.25 - 7.45 (m, 5 H) 6.92 (q, *J*=8.4 Hz, 1 H) 6.27 - 6.43 (m, 1 H) 5.98 - 6.10 (m, 2
 H) 5.82 - 5.98 (m, 2 H) 5.15 (br d, *J*=13.2 Hz, 1 H) 4.96 - 5.10 (m, 2 H) 4.81 - 4.92 (m,
 1 H) 4.30 (br t, *J*=10.4 Hz, 1 H) 1.76 - 2.00 (m, 1 H) 0.92 (br d, *J*=6.3 Hz, 3 H) 0.75 (br
 d, *J*=6.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.29 min, MH⁺ 494

[α]_D²⁰: -311.32 ° (c 0.106, DMF)

Chiral HPLC (method HPLC-A): Rt 4.56 min, chiral purity 100%

Compound 128BB:

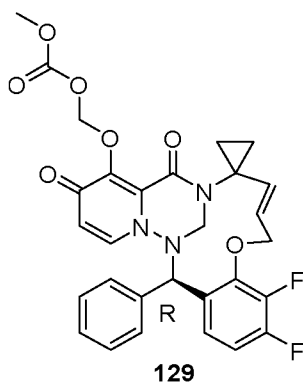
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.94 (br t, *J*=6.9 Hz, 1 H) 7.43 - 7.58 (m, 1 H) 7.03 - 7.35 (m, 6 H) 6.37 (ddd, *J*=15.4, 10.1, 5.4 Hz, 1 H) 5.75 (br dd, *J*=15.6, 7.1 Hz, 1 H) 5.47 (d, *J*=7.6 Hz, 1 H) 5.15 (s, 1 H) 5.08 (d, *J*=13.6 Hz, 1 H) 4.91 (dd, *J*=11.3, 5.4 Hz, 1 H) 4.85 (dd, *J*=11.0, 6.9 Hz, 1 H) 4.24 (d, *J*=13.6 Hz, 1 H) 4.08 (br t, *J*=10.9 Hz, 1 H) 1.63 - 1.81 (m, 1 H) 0.85 (d, *J*=6.3 Hz, 6 H)

LC/MS (method LC-C): Rt 3.12 min, MH⁺ 494

[α]_D²⁰: -555.17 ° (c 0.174, DMF)

Chiral HPLC (method HPLC-B): Rt 5.87 min, chiral purity 100%

Example 129: synthesis of (((18'R,E)-3',4'-difluoro-11',13'-dioxo-18'-phenyl-11',13'-dihydro-6'H,18'H-spiro[cyclopropane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin]-12'-yl)oxy)methyl methyl carbonate (Compound 129)



Compounds 120 was synthesized according to the procedure described in example 120

Compound 129:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (br t, *J*=6.9 Hz, 1 H) 7.44 - 7.57 (m, 1 H) 7.29 (d, *J*=7.6 Hz, 1 H) 7.02 - 7.26 (m, 5 H) 6.29 - 6.46 (m, 1 H) 5.93 - 6.14 (m, 1 H) 5.74 - 5.78 (m, 1 H) 5.70 (d, *J*=7.9 Hz, 1 H) 5.53 (d, *J*=6.3 Hz, 1 H) 5.28 (s, 1 H) 5.10 (d, *J*=13.9 Hz, 1 H) 4.87 (br dd, *J*=11.0, 6.6 Hz, 1 H) 4.25 (br t, *J*=9.6 Hz, 1 H) 4.19 (d, *J*=13.9 Hz, 1 H) 3.78 (s, 3 H) 1.25 - 1.34 (m, 1 H) 1.16 (dt, *J*=9.7, 6.3 Hz, 1 H) 0.79 - 0.87 (m, 1 H) 0.73 (dq, *J*=7.6, 4.9 Hz, 1 H)

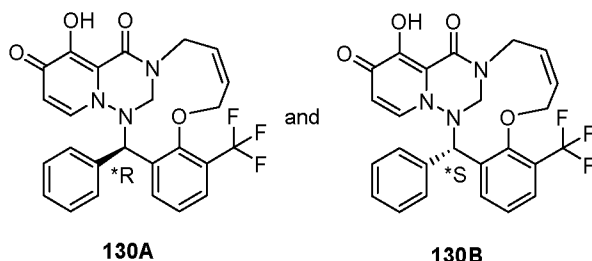
LC/MS (method LC-A): Rt 2.76 min, MH⁺ 566

[α]_D²⁰: -491.18 ° (c 0.170, DMF)

Chiral HPLC (method HPLC-A and B): **One peak observed**

Example 130: synthesis of (18'R,Z)-12-hydroxy-18-phenyl-4-(trifluoromethyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-

11,13-dione (Compound **130A**) and (18*S,Z)-12-hydroxy-18-phenyl-4-(trifluoromethyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **130B**)



Compounds **130A** and **130B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-(trifluoromethyl)benzene (synthesized as **74c** from 2-hydroxy-3-(trifluoromethyl)-benzaldehyde [CAS 336628-67-2]).

Compound **130A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.33 - 11.48 (m, 1 H) 8.44 (br d, *J*=7.6 Hz, 1 H) 7.79 (br d, *J*=7.6 Hz, 1 H) 7.61 (br t, *J*=7.9 Hz, 1 H) 6.94 - 7.31 (m, 6 H) 6.17 - 6.44 (m, 1 H) 5.86 - 6.11 (m, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.40 (s, 1 H) 5.19 (br d, *J*=13.9 Hz, 1 H) 4.97 (br dd, *J*=10.6, 6.5 Hz, 1 H) 4.85 (br dd, *J*=14.0, 4.3 Hz, 1 H) 4.36 (br d, *J*=13.9 Hz, 1 H) 4.07 - 4.27 (m, 1 H) 3.23 (br dd, *J*=14.2, 7.6 Hz, 1 H)

LC/MS (method LC-C): Rt 2.78 min, MH⁺ 484

[α]_D²⁰: -600.00 ° (c 0.205, DMF)

Chiral HPLC (method HPLC-A): Rt 4.31 min, chiral purity 100%

Compound **130B**:

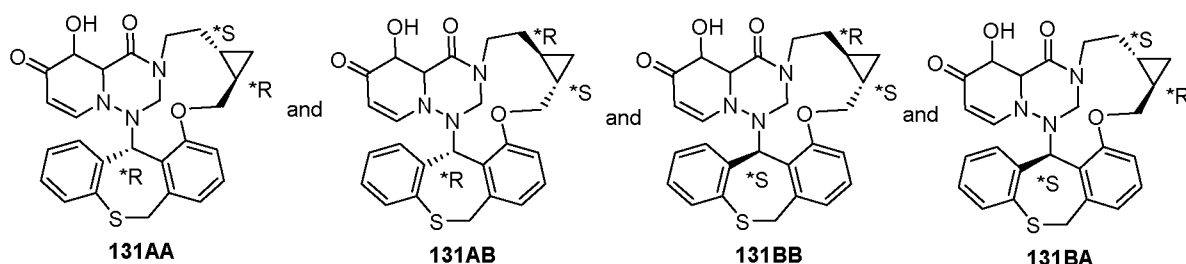
LC/MS (method LC-C): Rt 2.78 min, MH⁺ 484

[α]_D²⁰: +600.80 ° (c 0.25, DMF)

Chiral HPLC (method HPLC-A): Rt 4.80 min, chiral purity 100%

Example 131: synthesis of (1*R,13*S,15*R)-7-hydroxy-17-oxa-24-thia-2,3,10-triazaheptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **131AA**), (1*R,13*R,15*S)-7-hydroxy-17-oxa-24-thia-2,3,10-triazaheptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **131AB**), (1*S,13*R,15*S)-7-hydroxy-17-oxa-24-thia-2,3,10-

triazahaptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-
 4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **131BB**) and
 (1*S,13*S,15*R)-7-hydroxy-17-oxa-24-thia-2,3,10-
 triazahaptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-
 4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **131BA**)



Compounds **131AA**, **131AB**, **131BB** and **131BA** were synthesized according to the
 procedures described in example **87** starting from aminoethyl-cyclopropane-methanol
 [CAS 2086269-44-3].

Compound **131AA**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.48 - 12.44 (m, 1 H) 7.31 (t, *J*=7.9 Hz, 1 H)
 7.10 - 7.17 (m, 2 H) 7.05 - 7.09 (m, 1 H) 7.02 (dd, *J*=7.9, 3.5 Hz, 2 H) 6.82 - 6.89 (m, 1
 H) 6.76 - 6.81 (m, 1 H) 6.21 (s, 1 H) 5.63 (d, *J*=13.2 Hz, 1 H) 5.56 (br d, *J*=7.6 Hz, 1
 H) 5.00 (br d, *J*=12.9 Hz, 1 H) 4.65 (dd, *J*=12.0, 3.5 Hz, 1 H) 4.34 (d, *J*=12.9 Hz, 1 H)
 3.83 (d, *J*=13.6 Hz, 1 H) 3.63 - 3.72 (m, 1 H) 3.55 (br t, *J*=11.5 Hz, 1 H) 2.79 (br t,
J=12.1 Hz, 1 H) 1.91 (br d, *J*=14.8 Hz, 1 H) 1.65 - 1.80 (m, 1 H) 1.16 - 1.29 (m, 1 H)
 0.41 - 0.52 (m, 1 H) 0.37 (dt, *J*=8.7, 4.5 Hz, 1 H) 0.25 (dt, *J*=8.7, 4.5 Hz, 1 H)

LC/MS (method LC-C): Rt 2.93 min, MH⁺ 488

[α]_D²⁰: -83.75 ° (c 0.16, DMF)

Chiral HPLC (method HPLC-B): Rt 6.68 min, chiral purity 100%

Compound **131AB**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.32 - 12.35 (m, 1 H) 7.26 - 7.31 (m, 1 H) 7.20
 (d, *J*=8.2 Hz, 1 H) 7.04 - 7.10 (m, 1 H) 7.00 - 7.03 (m, 1 H) 6.98 (d, *J*=7.6 Hz, 1 H)
 6.95 (d, *J*=7.6 Hz, 1 H) 6.77 (t, *J*=6.9 Hz, 1 H) 6.68 (d, *J*=7.3 Hz, 1 H) 6.03 (s, 1 H)
 5.56 (d, *J*=13.6 Hz, 1 H) 5.52 (d, *J*=7.6 Hz, 1 H) 4.88 - 5.00 (m, 2 H) 4.05 (d, *J*=13.2
 Hz, 1 H) 3.74 (d, *J*=13.6 Hz, 1 H) 3.66 - 3.72 (m, 1 H) 3.11 - 3.18 (m, 1 H) 2.45 - 2.55
 (m, 2 H) 0.97 - 1.07 (m, 1 H) 0.89 - 0.96 (m, 1 H) 0.81 - 0.88 (m, 1 H) 0.65 (dt, *J*=8.3,
 4.2 Hz, 1 H) 0.42 - 0.51 (m, 1 H)

LC/MS (method LC-C): Rt 2.94 min, MH⁺ 488

$[\alpha]_D^{20}$: -251.11 ° (c 0.135, DMF)

Chiral HPLC (method HPLC-B): Rt 6.60 min, chiral purity 100%

Compound 131BB:

5 LC/MS (method LC-C): Rt 2.93 min, MH^+ 488

$[\alpha]_D^{20}$: +149.22 ° (c 0.128, DMF)

Chiral HPLC (method HPLC-B): Rt 5.21 min, chiral purity 100%

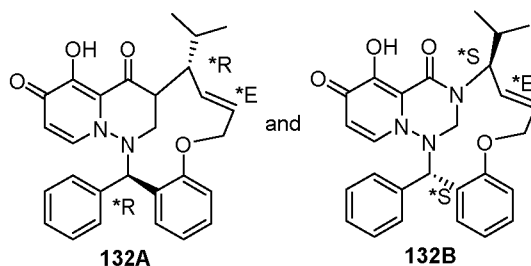
Compound 131BA:

10 LC/MS (method LC-C): Rt 2.94 min, MH^+ 488

$[\alpha]_D^{20}$: +249.52 ° (c 0.105, DMF)

Chiral HPLC (method HPLC-B): Rt 5.60 min, chiral purity 100%

15 Example 132: synthesis of (9*R,18*R,*E)-12-hydroxy-9-isopropyl-18-phenyl-9,10-dihydro-6H,18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6]diazacyclotridecine-11,13-dione (Compound **132A**) and (9*S,18*S,*E)-12-hydroxy-9-isopropyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **132B**)



Compounds **132A** and **132B** were synthesized according to the procedures described in example 39 starting from intermediate 5-hydroxy-3-(4-methylpent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (see example 124).

Compound 132A:

LC/MS (method LC-C): Rt 2.99 min, MH^+ 458

$[\alpha]_D^{20}$: +649.62 ° (c 0.133, DMF)

Chiral HPLC (method HPLC-B): Rt 4.95 min, chiral purity 100%

Compound 132B:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 10.47 - 11.84 (m, 1 H) 8.08 (dd, $J=7.7$, 1.4 Hz, 1 H) 7.44 (td, $J=7.7$, 1.6 Hz, 1 H) 7.31 - 7.39 (m, 1 H) 7.07 - 7.28 (m, 7 H) 6.31 (ddd,

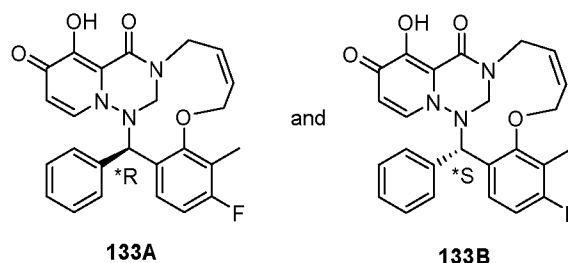
$J=15.7, 10.0, 5.5$ Hz, 1 H) 5.47 (d, $J=7.9$ Hz, 1 H) 5.40 (dd, $J=15.8, 7.3$ Hz, 1 H) 5.21 (s, 1 H) 5.06 (d, $J=13.6$ Hz, 1 H) 4.80 - 4.92 (m, 2 H) 4.21 (d, $J=13.6$ Hz, 1 H) 4.10 (t, $J=10.9$ Hz, 1 H) 1.58 - 1.77 (m, 1 H) 0.83 (t, $J=6.1$ Hz, 6 H)

LC/MS (method LC-C): Rt 2.98 min, MH^+ 458

5 $[\alpha]_D^{20}$: -610.17 ° (c 0.118, DMF)

Chiral HPLC (method HPLC-B): Rt 6.17 min, chiral purity 100%

Example 133: synthesis of (18^{*R,Z})-3-fluoro-12-hydroxy-4-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **133A**) and (18^{*S,Z})-3-fluoro-12-hydroxy-4-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **133B**)



Compounds **133A** and **133B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-4-fluoro-3-methylbenzene (synthesized as **74c** from 4-fluoro-2-hydroxy-3-methyl-benzaldehyde [CAS 775337-99-0]).

Compound **133A**:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.93 (br t, $J=7.7$ Hz, 1 H) 6.99 - 7.28 (m, 7 H) 6.12 - 6.37 (m, 1 H) 5.78 - 5.94 (m, 1 H) 5.47 (d, $J=7.6$ Hz, 1 H) 5.25 (s, 1 H) 5.13 (d, $J=13.9$ Hz, 1 H) 4.73 - 4.91 (m, 2 H) 4.32 (d, $J=13.9$ Hz, 1 H) 4.08 (br t, $J=8.4$ Hz, 1 H) 3.21 (br dd, $J=14.2, 7.6$ Hz, 1 H) 2.12 (d, $J=1.6$ Hz, 3 H)

LC/MS (method LC-C): Rt 2.74 min, MH^+ 448

$[\alpha]_D^{20}$: -624.63 ° (c 0.134, DMF)

Chiral HPLC (method HPLC-B): Rt 5.38 min, chiral purity 100%

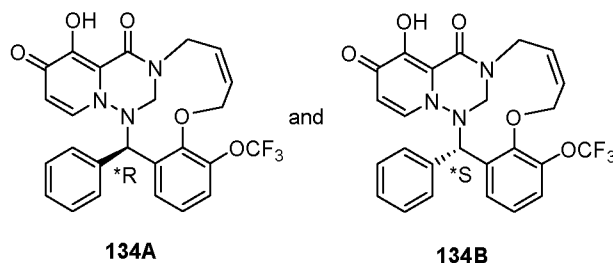
Compound **133B**:

LC/MS (method LC-C): Rt 2.74 min, MH^+ 448

$[\alpha]_D^{20}$: +674.22 ° (c 0.128, DMF)

Chiral HPLC (method HPLC-B): Rt 4.80 min, chiral purity 100%

Example 134: synthesis of (18*R,Z)-12-hydroxy-18-phenyl-4-(trifluoromethoxy)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **134A**) and (18*S,Z)-12-hydroxy-18-phenyl-4-(trifluoromethoxy)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **134B**)



Compounds **134A** and **134B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-(trifluoromethoxy)benzene (synthesized as **74c** from 2-hydroxy-3-(trifluoromethoxy)benzaldehyde [CAS 497959-31-9]).

Compound 134A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.14 (br d, *J*=3.8 Hz, 1 H) 7.43 - 7.59 (m, 2 H) 6.97 - 7.36 (m, 6 H) 6.13 - 6.34 (m, 1 H) 5.80 - 6.10 (m, 1 H) 5.48 (d, *J*=7.9 Hz, 1 H) 5.31 (br s, 1 H) 5.14 (d, *J*=13.6 Hz, 1 H) 4.68 - 4.93 (m, 2 H) 4.26 (br d, *J*=13.9 Hz, 2 H) 3.21 (br dd, *J*=14.0, 8.0 Hz, 1 H)

LC/MS (method LC-C): Rt 2.86 min, MH⁺ 500

[α]_D²⁰: -644.53 ° (c 0.137, DMF)

Chiral HPLC (method HPLC-A): Rt 4.19 min, chiral purity 100%

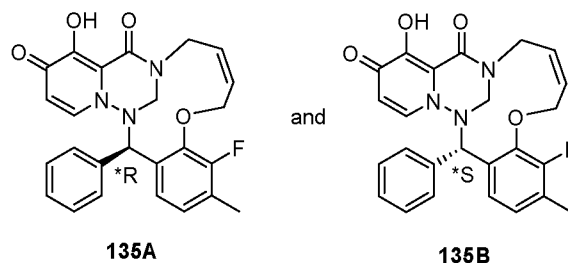
Compound 134B:

LC/MS (method LC-C): Rt 2.86 min, MH⁺ 500

[α]_D²⁰: +618.18 ° (c 0.154, DMF)

Chiral HPLC (method HPLC-A): Rt 4.61 min, chiral purity 100%

Example 135: synthesis of (18*R,Z)-4-fluoro-12-hydroxy-3-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **135A**) and (18*S,Z)-4-fluoro-12-hydroxy-3-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **135B**)



Compounds **135A** and **135B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3-fluoro-4-methylbenzene (synthesized as **74c** from 3-fluoro-2-hydroxy-4-methyl-benzaldehyde [CAS 1287718-64-8]).

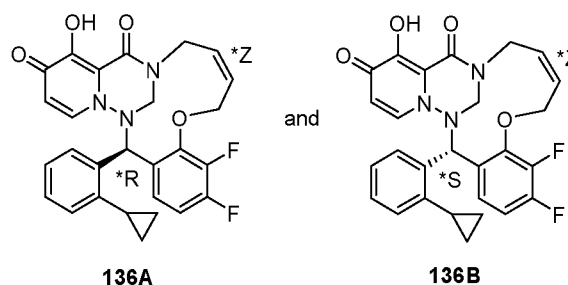
Compound 135A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.44 - 11.39 (m, 1 H) 7.78 (br d, *J*=7.9 Hz, 1 H) 7.28 (t, *J*=7.6 Hz, 1 H) 6.97 - 7.24 (m, 6 H) 6.14 - 6.32 (m, 1 H) 5.83 - 6.07 (m, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.23 (s, 1 H) 5.12 (d, *J*=13.9 Hz, 1 H) 4.71 - 4.89 (m, 2 H) 4.29 (d, *J*=13.9 Hz, 1 H) 4.15 - 4.25 (m, 1 H) 3.21 (dd, *J*=13.9, 7.9 Hz, 1 H) 2.27 (s, 3 H)
LC/MS (method LC-C): Rt 2.76 min, MH⁺ 448
[α]_D²⁰: -659.18 ° (c 0.245, DMF)

Compound 135B:

LC/MS (method LC-C): Rt 2.76 min, MH⁺ 448
[α]_D²⁰: +578.38 ° (c 0.185, DMF)

Example 136: synthesis (18^{*}R, *Z)-18-(2-cyclopropylphenyl)-3,4-difluoro-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **136A**) and (18^{*}S, *Z)-18-(2-cyclopropylphenyl)-3,4-difluoro-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **136B**)



Compounds **136A** and **136B** were synthesized according to the procedures described in example **5** starting from intermediate 2-(allyloxy)-1-(chloro(2-cyclopropylphenyl)methyl)-3,4-difluorobenzene (synthesized as in example 123 from **74a**).

5

Compound 136A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.52 - 11.22 (m, 1 H) 7.87 - 8.08 (m, 1 H) 7.56 - 7.64 (m, 1 H) 7.44 - 7.54 (m, 1 H) 7.27 (br d, *J*=7.6 Hz, 1 H) 7.03 - 7.18 (m, 2 H) 6.75 - 6.84 (m, 1 H) 6.12 - 6.28 (m, 1 H) 5.88 - 6.10 (m, 2 H) 5.51 (d, *J*=7.6 Hz, 1 H) 5.17 (d, *J*=13.9 Hz, 1 H) 4.85 - 4.92 (m, 1 H) 4.81 (br dd, *J*=13.9, 4.4 Hz, 1 H) 4.27 - 4.42 (m, 2 H) 3.23 (dd, *J*=14.0, 8.0 Hz, 1 H) 1.97 - 2.06 (m, 1 H) 0.85 - 1.00 (m, 2 H) 0.74 - 0.82 (m, 1 H) 0.01 - 0.08 (m, 1 H)

LC/MS (method LC-C): Rt 2.89 min, MH⁺ 492

[α]_D²⁰: -648.00 ° (c 0.125, DMF)

15 Chiral HPLC (method HPLC-A and B): **No separation observed**

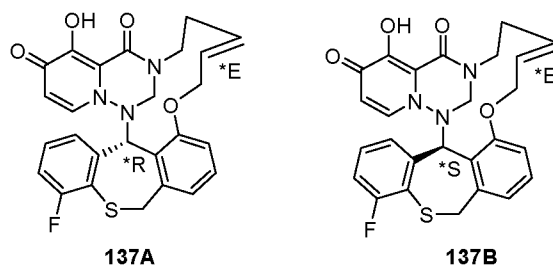
Compound 136B:

LC/MS (method LC-C): Rt 2.89 min, MH⁺ 492

[α]_D²⁰: +610.49 ° (c 0.143, DMF)

20 Chiral HPLC (method HPLC-A and B): **No separation observed**

Example 137: synthesis of (1^{*}R,13^{*}E)-25-fluoro-7-hydroxy-16-oxa-23-thia-2,3,10-triazahexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione (Compound **137A**) and (1^{*}S,13^{*}E)-25-fluoro-7-hydroxy-16-oxa-23-thia-2,3,10-triazahexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione (Compound **137B**)



30 Compounds **137A** and **137B** were synthesized according to the procedures described in example **37** starting from intermediate 10-(allyloxy)-11-chloro-4-fluoro-6,11-dihydrodibenzo[b,e]thiepine (synthesized as **88n** from 2-methoxy-methyl ester-benzoic acid [CAS 606-45-1] and 2-fluoro-benzenethiol [CAS 2557-78-0]).

Compound 137A:LC/MS (method LC-C): Rt 2.80 min, MH⁺ 492[α]_D²⁰: +62.81 ° (c 0.121, DMF)

5 Chiral HPLC (method HPLC-B): Rt 5.38 min, chiral purity 100%

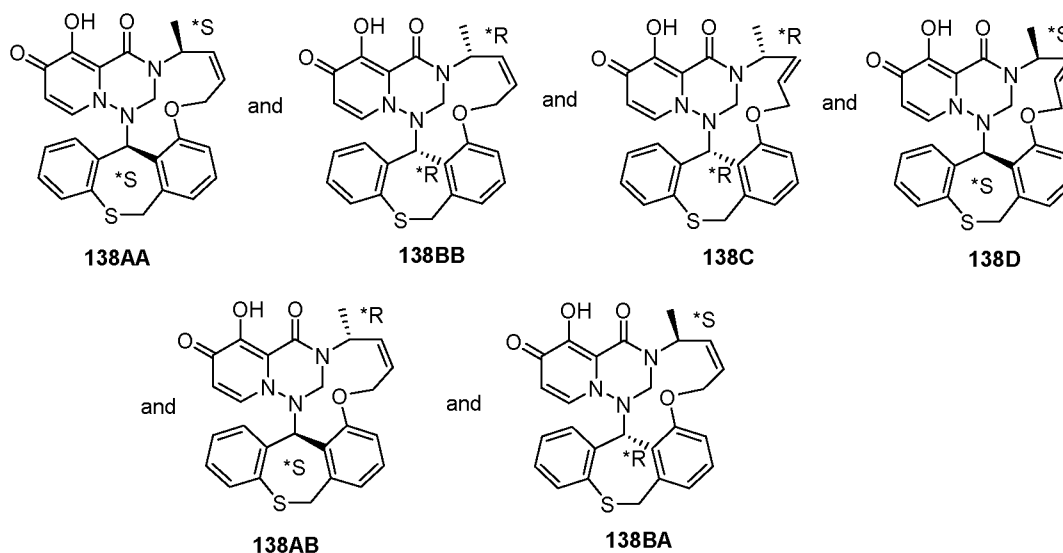
Compound 137B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.75 (br s, 1 H) 7.39 (t, *J*=7.9 Hz, 1 H) 7.24 (d, *J*=7.6 Hz, 1 H) 7.03 - 7.13 (m, 3 H) 6.84 - 6.92 (m, 1 H) 6.48 (d, *J*=7.9 Hz, 1 H) 6.16 (s, 1 H) 6.03 - 6.12 (m, 1 H) 5.96 (td, *J*=10.6, 4.1 Hz, 1 H) 5.75 (d, *J*=13.6 Hz, 1 H) 5.62 (d, *J*=7.9 Hz, 1 H) 4.95 (d, *J*=13.2 Hz, 1 H) 4.47 - 4.59 (m, 2 H) 4.20 - 4.34 (m, 2 H) 3.95 (d, *J*=13.2 Hz, 1 H) 2.85 (br d, *J*=14.2 Hz, 1 H) 2.12 - 2.32 (m, 2 H)

LC/MS (method LC-C): Rt 2.81 min, MH⁺ 492[α]_D²⁰: -161.05 ° (c 0.172, DMF)

15 Chiral HPLC (method HPLC-B): Rt 7.55 min, chiral purity 100%

Example 138: synthesis of (13*S,21a*S,Z)-16-hydroxy-13-methyl-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **138AA**), (13*R,21a*R,Z)-16-hydroxy-13-methyl-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **138BB**), (9*R,17a*R,E)-12-hydroxy-9-methyl-2,6,9,17a-tetrahydro-3,4-(epi-prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **138C**) and (9*S,17a*S,E)-12-hydroxy-9-methyl-2,6,9,17a-tetrahydro-3,4-(epi-prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **138D**) and (13*R,21a*S,Z)-16-hydroxy-13-methyl-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **138AB**) and (13*S,21a*R,Z)-16-hydroxy-13-methyl-6,10,13,21a-tetrahydro-7,8-(epi-prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **138BA**)



Compounds **138AA**, **138BB**, **138C**, **138D**, **138AB** and **138BA** were synthesized according to the procedures described in example **46** starting from **29c** and **37c**.

5

Compound 138AA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.41 (t, *J*=7.9 Hz, 1 H) 7.19 (d, *J*=7.6 Hz, 1 H) 7.02 - 7.15 (m, 4 H) 6.75 - 6.87 (m, 1 H) 6.53 (d, *J*=7.6 Hz, 1 H) 6.47 (br t, *J*=9.8 Hz, 1 H) 6.18 (dt, *J*=10.3, 6.8 Hz, 1 H) 6.07 (s, 1 H) 5.70 (d, *J*=13.9 Hz, 1 H) 5.60 (d, *J*=7.6 Hz, 1 H) 5.17 (d, *J*=13.2 Hz, 1 H) 4.77 (dd, *J*=10.4, 6.9 Hz, 1 H) 4.37 - 4.49 (m, 1 H) 4.30 (d, *J*=13.2 Hz, 1 H) 3.96 - 4.09 (m, 1 H) 3.79 (d, *J*=13.9 Hz, 1 H) 1.37 (d, *J*=6.3 Hz, 3 H)

LC/MS (method LC-C): Rt 2.84 min, MH⁺ 474

[α]_D²⁰: -170.83 ° (c 0.096, DMF)

Chiral HPLC (method HPLC-B): Rt 7.91 min, chiral purity 100%

Compound 138BB:

LC/MS (method LC-C): Rt 2.84 min, MH⁺ 474

[α]_D²⁰: +160.82 ° (c 0.097, DMF)

Chiral HPLC (method HPLC-B): Rt 4.75 min, chiral purity 100%

Compound 138C:

LC/MS (method LC-C): Rt 2.72 min, MH⁺ 474

[α]_D²⁰: +498.95 ° (c 0.191, DMF)

Chiral HPLC (method HPLC-B): Rt 6.61 min, chiral purity 100%

Compound 138D:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.83 - 12.19 (m, 1 H) 7.41 (t, *J*=7.9 Hz, 1 H) 7.33 (d, *J*=7.6 Hz, 1 H) 7.19 (dd, *J*=11.0, 7.9 Hz, 2 H) 7.07 - 7.13 (m, 1 H) 7.01 - 7.06 (m, 1 H) 6.78 - 6.89 (m, 2 H) 6.31 (ddd, *J*=15.7, 9.7, 5.5 Hz, 1 H) 5.82 (d, *J*=13.2 Hz, 1 H) 5.54 - 5.66 (m, 2 H) 5.43 (quin, *J*=6.8 Hz, 1 H) 5.33 (s, 1 H) 5.06 (d, *J*=13.2 Hz, 1 H) 4.88 (dd, *J*=11.2, 5.5 Hz, 1 H) 4.23 - 4.35 (m, 2 H) 3.87 (d, *J*=13.2 Hz, 1 H) 1.14 (d, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 2.72 min, MH⁺ 474

[α]_D²⁰: -500.00° (c 0.107, DMF)

Chiral HPLC (method HPLC-B): Rt 8.81 min, chiral purity 100%

Compound 138AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.34 - 7.45 (m, 2 H) 7.31 (br d, *J*=7.6 Hz, 1 H) 7.09 - 7.22 (m, 3 H) 6.86 (br t, *J*=7.1 Hz, 1 H) 6.70 (br d, *J*=7.6 Hz, 1 H) 6.08 - 6.18 (m, 1 H) 6.02 (s, 1 H) 5.64 - 5.77 (m, 3 H) 5.32 - 5.42 (m, 1 H) 4.88 - 5.07 (m, 3 H) 4.28 (br d, *J*=13.2 Hz, 1 H) 3.83 (br d, *J*=13.6 Hz, 1 H) 1.39 (br d, *J*=6.0 Hz, 3 H)

LC/MS (method LC-C): Rt 2.77 min, MH⁺ 474

[α]_D²⁰: -258.59° (c, DMF)

Chiral HPLC (method HPLC-A): Rt 7.38 min, chiral purity 100%

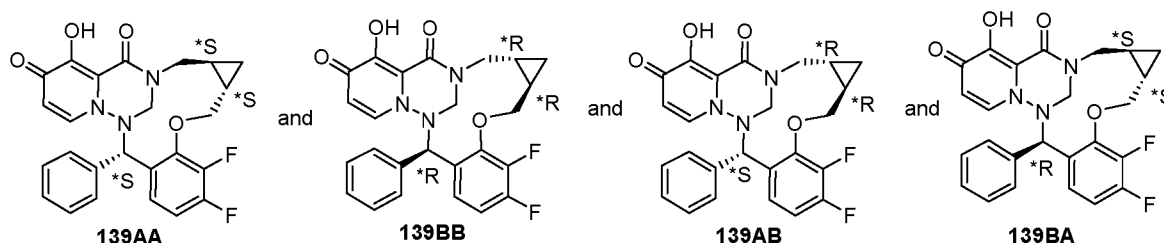
Compound 138BA:

LC/MS (method LC-C): Rt 2.77 min, MH⁺ 474

[α]_D²⁰: +277.53 ° (c 0.089, DMF)

Chiral HPLC (method HPLC-A): Rt 6.36 min, chiral purity 100%

Example 139: synthesis of (1a*S,8*S,17a*S)-4,5-difluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **139AA**), (1a*R,8*R,17a*R)-4,5-difluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **139BB**), (1a*R,8*S,17a*R)-4,5-difluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **139AB**) and (1a*S,8*R,17a*S)-4,5-difluoro-14-hydroxy-8-phenyl-1a,2,17,17a-tetrahydro-1H,8H-9,16-methanobenzo[b]cyclopropa[k]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-13,15-dione (Compound **139BA**)



Compounds **139AA**, **139BB**, **139AB** and **139BA** were synthesized according to the procedures described in example **80** starting from intermediate 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene **74c**.

Compound 139AA:

LC/MS (method LC-C): Rt 2.81 min, MH^+ 466

$[\alpha]_D^{20}$: +265.85° (c 0.164, DMF)

Chiral HPLC (method HPLC-B): Rt 4.43 min, chiral purity 100%

Compound 139BB:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 10.64 - 11.63 (m, 1 H) 7.87 - 7.95 (m, 1 H) 7.36 - 7.50 (m, 1 H) 7.04 - 7.35 (m, 6 H) 5.92 (s, 1 H) 5.50 (d, $J=7.6$ Hz, 1 H) 5.09 (d, $J=13.6$ Hz, 1 H) 4.89 (dd, $J=12.8, 4.3$ Hz, 1 H) 4.57 (d, $J=13.6$ Hz, 1 H) 3.58 (dd, $J=14.5, 10.7$ Hz, 1 H) 3.18 - 3.27 (m, 2 H) 1.29 - 1.53 (m, 1 H) 1.01 (ddt, $J=14.0, 9.5, 4.5, 4.5$ Hz, 1 H) 0.71 (dt, $J=8.7, 4.5$ Hz, 1 H) 0.54 - 0.64 (m, 1 H)

LC/MS (method LC-C): Rt 2.81 min, MH^+ 466

$[\alpha]_D^{20}$: -260.99° (c 0.182, DMF)

Chiral HPLC (method HPLC-B): Rt 5.78 min, chiral purity 99.07%

Compound 139AB:

LC/MS (method LC-C): Rt 2.80 min, MH^+ 466

$[\alpha]_D^{20}$: +441.9° (c 0.253, DMF)

Chiral HPLC (method HPLC-A): Rt 8.62 min, chiral purity 100%

Compound 139BA:

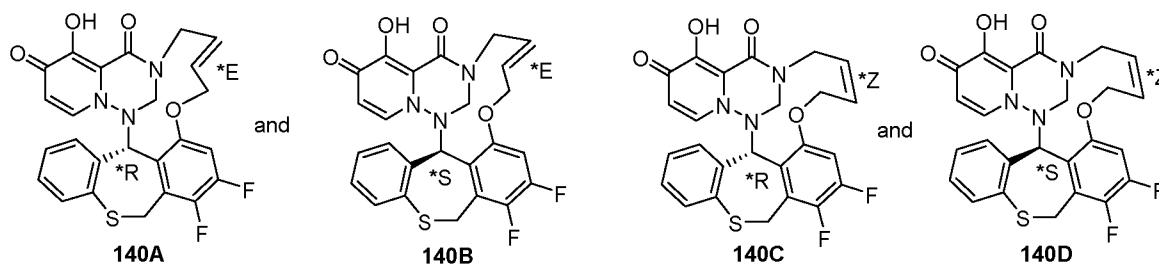
^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 10.64 - 11.62 (m, 1 H) 8.04 - 8.15 (m, 1 H) 7.40 - 7.52 (m, 2 H) 7.19 (br s, 5 H) 5.97 (s, 1 H) 5.50 (d, $J=7.7$ Hz, 1 H) 5.14 (d, $J=13.6$ Hz, 1 H) 4.75 (dd, $J=12.5, 3.2$ Hz, 1 H) 4.34 - 4.46 (m, 2 H) 3.47 (t, $J=12.0$ Hz, 1 H) 2.14 (dd, $J=13.9, 11.2$ Hz, 1 H) 1.36 - 1.52 (m, 1 H) 1.20 (td, $J=8.0, 4.5$ Hz, 1 H) 0.57 (dt, $J=8.9, 4.5$ Hz, 1 H) 0.40 (dt, $J=9.2, 4.7$ Hz, 1 H)

LC/MS (method LC-C): Rt 2.80 min, MH^+ 466

$[\alpha]_D^{20}$: -424.27 ° (c 0.206, DMF)

Chiral HPLC (method HPLC-A): Rt 4.81 min, chiral purity 100%

Example 140: synthesis of (17a*R,*E)-24,25-difluoro-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi)prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **140A**), (17a*S,*E)-24,25-difluoro-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi)prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **140B**), (21a*R,*Z)-24,25-difluoro-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epi)prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (compound **140C**) and (21a*S,*Z)-24,25-difluoro-16-hydroxy-6,10,13,21a-tetrahydro-7,8-(epi)prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **140D**)



Compounds **140A**, **140B**, **140C** and **140D** were synthesized according to the procedures described in example **88** starting from intermediate **5d**.

Compound **140A**:

LC/MS (method LC-C): Rt 2.79 min, MH^+ 496

$[\alpha]_D^{20}$: +476.06° (c 0.071, DMF)

Chiral HPLC (method HPLC-B): Rt 5.58 min, chiral purity 100%

Compound **140B**:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.50 (br dd, $J=11.7, 7.3$ Hz, 1 H) 7.28 (d, $J=7.6$ Hz, 1 H) 7.11 - 7.19 (m, 1 H) 7.05 - 7.10 (m, 1 H) 6.89 (t, $J=7.3$ Hz, 1 H) 6.77 - 6.85 (m, 1 H) 6.23 (dt, $J=15.5, 7.5$ Hz, 1 H) 5.96 - 6.12 (m, 1 H) 5.70 (br d, $J=14.2$ Hz, 1 H) 5.62 (d, $J=7.6$ Hz, 1 H) 5.36 (s, 1 H) 5.14 (d, $J=13.9$ Hz, 1 H) 4.71 - 4.83 (m, 2 H) 4.49 (br t, $J=9.5$ Hz, 1 H) 4.37 (d, $J=13.9$ Hz, 1 H) 4.11 (d, $J=13.9$ Hz, 1 H) 3.12 (br dd, $J=13.9, 8.5$ Hz, 1 H)

LC/MS (method LC-C): Rt 2.78 min, MH^+ 496

$[\alpha]_D^{20}$: -528.75 ° (c 0.08, DMF)

Chiral HPLC (method HPLC-B): Rt 8.09 min, chiral purity 100%

Compound 140C:

LC/MS (method LC-C): Rt 2.87 min, MH^+ 496

5 $[\alpha]_D^{20}$: +306.67 ° (c 0.060, DMF)

Chiral HPLC (method HPLC-B): Rt 5.07 min, chiral purity 100%

Compound 140D:

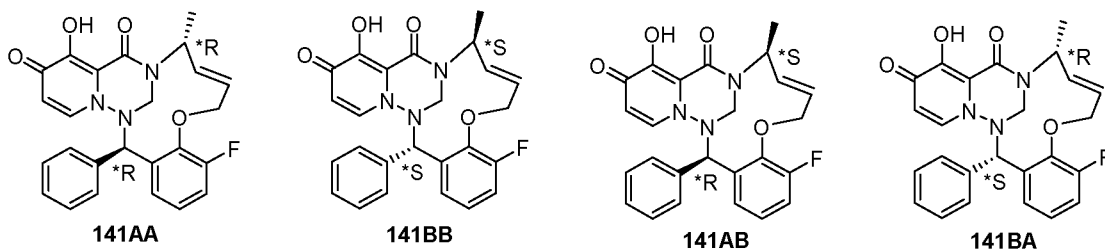
^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.78 - 12.11 (m, 1 H) 7.47 (dd, $J=12.0$, 7.1 Hz, 1 H) 7.24 (d, $J=7.7$ Hz, 1 H) 7.07 - 7.19 (m, 2 H) 6.80 - 6.90 (m, 1 H) 6.57 (d, $J=7.6$ Hz, 1 H) 6.37 - 6.49 (m, 1 H) 6.29 (dt, $J=10.4$, 7.4 Hz, 1 H) 6.01 (s, 1 H) 5.55 - 5.68 (m, 2 H) 5.02 (d, $J=13.4$ Hz, 1 H) 4.86 (dd, $J=10.6$, 6.8 Hz, 1 H) 4.57 (dd, $J=10.4$, 7.9 Hz, 1 H) 4.41 (d, $J=13.4$ Hz, 1 H) 4.18 (dd, $J=13.5$, 7.5 Hz, 1 H) 4.03 (d, $J=14.4$ Hz, 1 H) 3.81 (dd, $J=13.4$, 8.6 Hz, 1 H)

15 LC/MS (method LC-C): Rt 2.88 min, MH^+ 496

$[\alpha]_D^{20}$: -265.79 ° (c 0.076, DMF)

Chiral HPLC (method HPLC-B): Rt 9.82 min, chiral purity 100%

Example 141: synthesis (9 $^*R$,18 $^*R$,E)-4-fluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **141AA**), (9 $^*S$,18 $^*S$,E)-4-fluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **141BB**), (9 $^*S$,18 $^*R$,E)-4-fluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **141AB**) and (9 $^*R$,18 $^*S$,E)-4-fluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **141BA**)



Compounds **141AA**, **141BB**, **141AB** and **141BA** were synthesized according to the procedures described in example 29 starting from intermediate **61b**.

Compound 141AA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.54 - 11.62 (m, 1 H) 7.93 (d, *J*=7.7 Hz, 1 H)
7.31 - 7.50 (m, 2 H) 7.04 - 7.28 (m, 6 H) 6.35 (ddd, *J*=15.4, 10.1, 5.5 Hz, 1 H) 5.37 -
5.62 (m, 3 H) 5.20 (s, 1 H) 5.06 (d, *J*=13.6 Hz, 1 H) 4.88 (dd, *J*=11.3, 5.3 Hz, 1 H) 4.26
(d, *J*=13.7 Hz, 1 H) 4.00 (br t, *J*=10.8 Hz, 1 H) 1.15 (d, *J*=7.1 Hz, 3 H)

LC/MS (method LC-C): Rt 2.72 min, MH⁺ 448

[α]_D²⁰: -602.86 ° (c 0.175, DMF)

Chiral HPLC (method HPLC-A): Rt 8.25 min, chiral purity 100%

Compound 141BB:

LC/MS (method LC-C): Rt 2.72 min, MH⁺ 448

[α]_D²⁰: +613.41 ° (c 0.179, DMF)

Chiral HPLC (method HPLC-A): Rt 5.97 min, chiral purity 100%

Compound 141AB:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.83 - 11.25 (m, 1 H) 7.97 (d, *J*=7.7 Hz, 1 H)
7.28 - 7.46 (m, 3 H) 7.00 - 7.25 (m, 5 H) 6.39 - 6.58 (m, 1 H) 5.81 - 6.02 (m, 1 H) 5.50
(d, *J*=7.7 Hz, 1 H) 5.42 (s, 1 H) 5.19 (d, *J*=13.9 Hz, 1 H) 4.59 - 4.71 (m, 1 H) 4.46 -
4.58 (m, 1 H) 4.22 (d, *J*=13.9 Hz, 1 H) 3.65 - 3.86 (m, 1 H) 1.75 (d, *J*=7.0 Hz, 3 H)

LC/MS (method LC-C): Rt 2.75 min, MH⁺ 448

[α]_D²⁰: -710.91 ° (c 0.220, DMF)

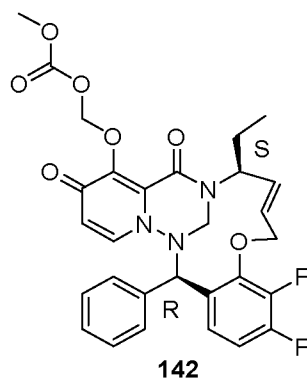
Compound 141BA:

LC/MS (method LC-C): Rt 2.75 min, MH⁺ 448

[α]_D²⁰: +717.45 ° (c 0.212, DMF)

Example 142: synthesis of (((9*S*,18*R*,*E*)-9-ethyl-3,4-difluoro-11,13-dioxo-18-phenyl-
6,9,11,13-tetrahydro-18*H*-10,17-methanobenzo[*b*]pyrido[1,2-
f][1]oxa[5,6,9]triazacyclotridecin-12-yl)oxy)methyl methyl carbonate (Compound **142**)

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Compounds **142** was synthesized according to the procedure described in example **120** starting from compound **101AA**.

5 Compound 142:

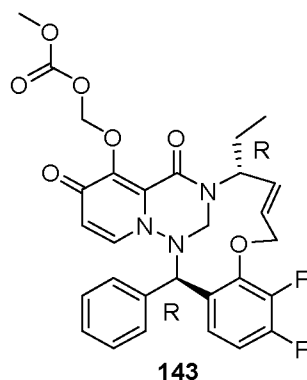
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.93 (br t, *J*=6.9 Hz, 1 H) 7.44 - 7.59 (m, 1 H) 7.31 (d, *J*=7.7 Hz, 1 H) 6.94 - 7.26 (m, 5 H) 6.30 (ddd, *J*=15.6, 10.1, 5.3 Hz, 1 H) 5.74 (d, *J*=6.6 Hz, 1 H) 5.69 (d, *J*=7.8 Hz, 1 H) 5.59 - 5.67 (m, 1 H) 5.56 (d, *J*=6.5 Hz, 1 H) 5.16 (q, *J*=7.4 Hz, 1 H) 5.10 (s, 1 H) 5.01 (d, *J*=13.8 Hz, 1 H) 4.92 (dd, *J*=11.2, 5.4 Hz, 1 H) 4.17 (d, *J*=13.8 Hz, 1 H) 4.07 (br t, *J*=10.9 Hz, 1 H) 3.77 (s, 3 H) 1.35 - 1.60 (m, 2 H) 0.81 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-A): Rt 2.84 min, MH⁺ 568

[α]_D²⁰: -500.62 ° (c 0.161, DMF)

Chiral HPLC (method HPLC-B): Rt 7.66 min, chiral purity 99.43%

Example 143: synthesis of (((9R,18R,E)-9-ethyl-3,4-difluoro-11,13-dioxo-18-phenyl-6,9,11,13-tetrahydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin-12-yl)oxy)methyl methyl carbonate (Compound **143**)



Compounds **143** was synthesized according to the procedure described in example **120** starting from compound **101AB**.

Compound 143:

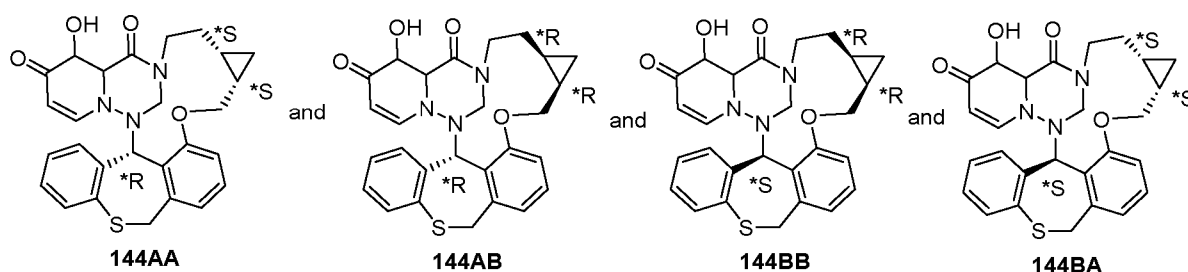
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.00 (br t, *J*=7.0 Hz, 1 H) 7.44 - 7.57 (m, 1 H) 7.40 (d, *J*=7.8 Hz, 1 H) 7.13 - 7.25 (m, 3 H) 6.91 - 7.12 (m, 2 H) 6.42 - 6.59 (m, 1 H) 5.87 - 6.08 (m, 1 H) 5.74 (d, *J*=6.5 Hz, 1 H) 5.68 (d, *J*=7.7 Hz, 1 H) 5.57 (d, *J*=6.5 Hz, 1 H) 5.38 (s, 1 H) 5.15 (d, *J*=14.1 Hz, 1 H) 4.63 - 4.73 (m, 1 H) 4.52 - 4.62 (m, 1 H) 4.17 (d, *J*=14.2 Hz, 1 H) 3.77 (s, 3 H) 3.35 - 3.42 (m, 1 H) 2.05 - 2.27 (m, 2 H) 0.84 (t, *J*=7.4 Hz, 3 H)

LC/MS (method LC-A): Rt 2.89 min, MH⁺ 568

[α]_D²⁰: -596.53° (c 0.173, DMF)

Chiral HPLC (method HPLC-B): Rt 5.44 min, chiral purity 98.79%

Example 144: synthesis of (1*R,13*S,15*S)-7-hydroxy-17-oxa-24-thia-2,3,10-triazaheptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **144AA**), (1*R,13*R,15*R)-7-hydroxy-17-oxa-24-thia-2,3,10-triazaheptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **144AB**), (1*S,13*R,15*R)-7-hydroxy-17-oxa-24-thia-2,3,10-triazaheptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **144BB**) and (1*S,13*S,15*S)-7-hydroxy-17-oxa-24-thia-2,3,10-triazaheptacyclo[16.12.1.12,10.03,8.013,15.022,31.025,30]dotriaconta-4,18,20,22(31),25(30),26,28-heptaene-6,9-dione (Compound **144BA**)



Compounds **144AA**, **144AB**, **144BB** and **144BA** were synthesized according to the procedures described in example **87** starting from intermediate trans-2-((1RS,2RS)-2-(((tert-butyl)diphenylsilyl)oxy)methyl)cyclopropyl)ethan-1-amine (synthesized as **87e** from trans-(1RS,2RS)cyclopropaneethanol, 2-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl] [CAS 2243217-26-5]).

Compound 144AA:LC/MS (method LC-C): Rt 3.00 min, MH⁺ 488[α]_D²⁰: +122.22 ° (c 0.063, DMF)

Chiral HPLC (method HPLC-B): Rt 5.87 min, chiral purity 100%

5

Compound 144AB:LC/MS (method LC-C): Rt 2.91 min, MH⁺ 488[α]_D²⁰: +220.59 ° (c 0.068, DMF)

Chiral HPLC (method HPLC-B): Rt 6.48 min, chiral purity 100%

10

Compound 144BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.23 - 12.74 (m, 1 H) 7.34 (t, *J*=7.9 Hz, 1 H) 7.25 (d, *J*=7.6 Hz, 1 H) 7.10 - 7.16 (m, 1 H) 7.05 - 7.10 (m, 1 H) 7.02 (d, *J*=7.6 Hz, 1 H) 6.93 (d, *J*=8.2 Hz, 1 H) 6.80 - 6.88 (m, 1 H) 6.69 (d, *J*=6.9 Hz, 1 H) 6.23 (s, 1 H) 5.71 (d, *J*=13.6 Hz, 1 H) 5.58 (d, *J*=7.9 Hz, 1 H) 4.93 (d, *J*=13.2 Hz, 1 H) 4.69 (dd, *J*=10.6, 4.3 Hz, 1 H) 4.14 - 4.35 (m, 2 H) 3.80 (d, *J*=13.2 Hz, 1 H) 3.25 (br d, *J*=11.0 Hz, 1 H) 2.80 (br d, *J*=14.2 Hz, 1 H) 1.66 (br d, *J*=15.4 Hz, 1 H) 1.43 - 1.58 (m, 1 H) 1.24 - 1.37 (m, 1 H) 1.05 - 1.19 (m, 1 H) 0.86 (td, *J*=8.7, 4.7 Hz, 1 H) 0.11 (q, *J*=5.4 Hz, 1 H)

20 LC/MS (method LC-C): Rt 3.00 min, MH⁺ 488[α]_D²⁰: -143.33 ° (c 0.06, DMF)

Chiral HPLC (method HPLC-B): Rt 8.67 min, chiral purity 100%

Compound 144BA:

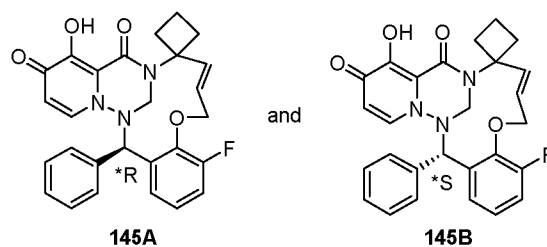
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.36 (t, *J*=7.9 Hz, 1 H) 7.30 (d, *J*=7.6 Hz, 1 H) 7.09 - 7.16 (m, 1 H) 6.99 - 7.09 (m, 3 H) 6.84 (t, *J*=7.1 Hz, 1 H) 6.67 (d, *J*=7.3 Hz, 1 H) 5.99 (s, 1 H) 5.76 (d, *J*=13.6 Hz, 1 H) 5.59 (d, *J*=7.6 Hz, 1 H) 5.00 (d, *J*=12.9 Hz, 1 H) 4.38 (br d, *J*=11.0 Hz, 1 H) 4.15 - 4.32 (m, 3 H) 3.81 (d, *J*=13.6 Hz, 1 H) 2.75 (br dd, *J*=13.9, 3.2 Hz, 1 H) 1.77 (br dd, *J*=14.2, 6.6 Hz, 1 H) 1.28 - 1.43 (m, 2 H) 0.92 - 1.03 (m, 1 H) 0.71 - 0.90 (m, 2 H)

30 LC/MS (method LC-C): Rt 2.91 min, MH⁺ 488[α]_D²⁰: -233.87 ° (c 0.062, DMF)

Chiral HPLC (method HPLC-B): Rt 11.08 min, chiral purity 100%

35 Example 145: synthesis of (18'*R,E)-4'-fluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **145A**), (18'*S,E)-4'-fluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-

[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione
(Compound **145B**)



5

Compounds **145A** and **145B** were synthesized according to the procedures described in example **146** starting from intermediates **146f** and **61b**.

Compound **145A**:

- 10 ^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.93 (br d, $J=7.6$ Hz, 1 H) 7.27 - 7.43 (m, 3 H) 7.01 - 7.22 (m, 5 H) 6.46 (br d, $J=15.2$ Hz, 1 H) 6.01 - 6.21 (m, 1 H) 5.49 (d, $J=7.6$ Hz, 1 H) 5.29 (s, 1 H) 5.13 (d, $J=13.7$ Hz, 1 H) 4.72 - 4.85 (m, 1 H) 4.42 - 4.56 (m, 1 H) 3.84 (d, $J=13.7$ Hz, 1 H) 2.80 - 2.92 (m, 1 H) 2.40 - 2.47 (m, 1 H) 1.98 - 2.15 (m, 2 H) 1.75 (q, $J=8.8$ Hz, 1 H) 1.52 - 1.67 (m, 1 H)
- 15 LC/MS (method LC-C): Rt 2.99 min, MH^+ 474
 $[\alpha]_{\text{D}}^{20}$: -664.47 ° (c 0.197, DMF)
 Chiral HPLC (method HPLC-A): Rt 10.57 min, chiral purity 100%

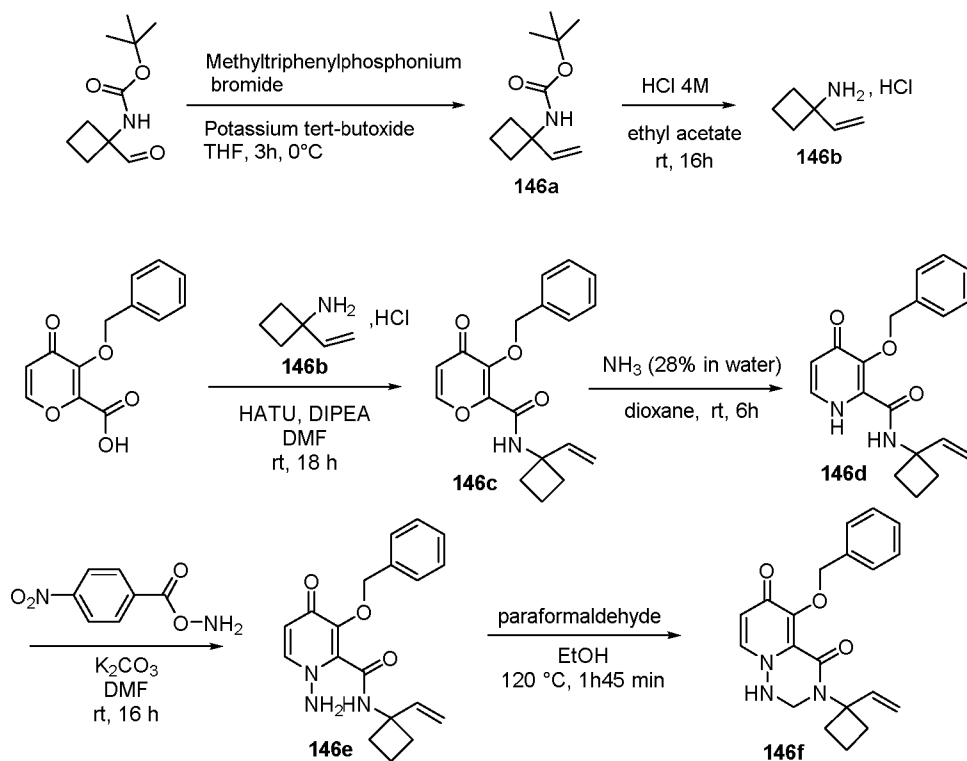
Compound **145B**:

- 20 LC/MS (method LC-C): Rt 2.99 min, MH^+ 474
 $[\alpha]_{\text{D}}^{20}$: +640.63 ° (c 0.224, DMF)
 Chiral HPLC (method HPLC-A): Rt 7.62 min, chiral purity 100%

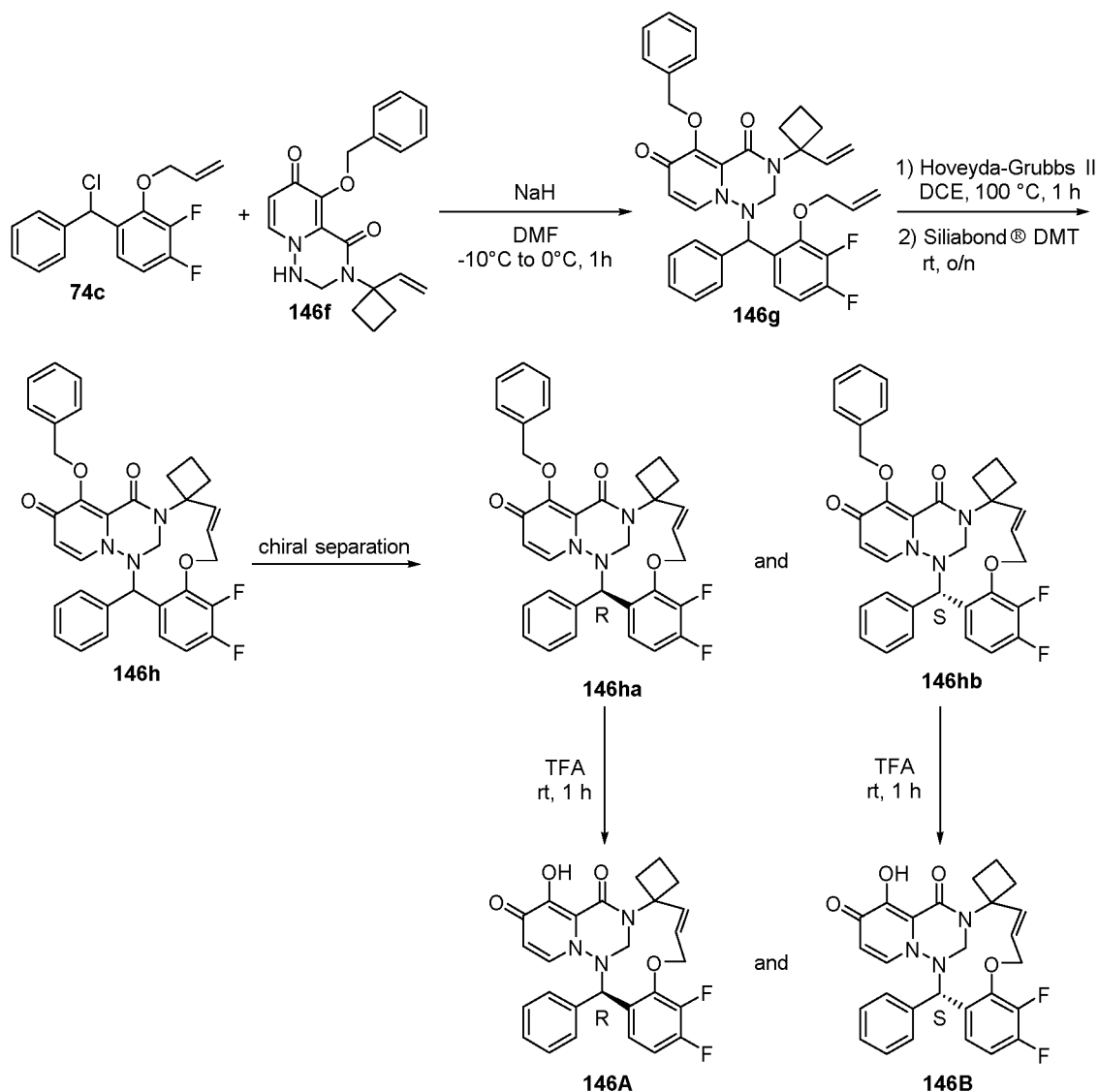
Example 146: synthesis of (18'R,E)-3',4'-difluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **146A**), (18'S,E)-3',4'-difluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **146B**)

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**Synthesis of intermediate 146a:**

To a solution of Methyltriphenylphosphonium bromide (499.135 g, 1397.261 mmol) in THF (3000 ml) was added Potassium tert-butoxide (146.990 g, 1309.932 mmol) at 0°C under N₂. The reaction was stirred for 30 min at 0°C. To the reaction was added tert-butyl 1-formylcyclobutylcarbamate (174 g, 873.288 mmol) in THF (500 mL). The reaction was stirred for 3 hours at 0°C. Sat. NaCl (1000 mL) was added and the reaction mixture was extracted with EtOAc (3 x 1000 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (0-10% EtOAc / Petroleum Ether) to afford tert-butyl 1-vinylcyclobutylcarbamate (intermediate **146a**, 160 g) as white solid.

Synthesis of intermediate 146b:

To a solution of tert-butyl 1-vinylcyclobutylcarbamate **146a** (160 g, 811.055 mmol) in ethyl acetate (300 ml) was added hydrogen chloride (4 M in ethyl acetate, 811.077 ml) at 0°C. The reaction was stirred overnight at rt. To the stirred reaction was added n-hexane (1.5 L), and the resulting mixture was filtered to afford intermediate 1-vinylcyclobutanamine hydrochloride (intermediate **146b**, 100 g) as white solid.

Synthesis of intermediate 146c:

Under N₂, a mixture of 3-(benzyloxy)-4-oxo-4H-pyran-2-carboxylic acid [CAS 119736-16-2] (20 g, 81 mmol), 1-vinylcyclobutan-1-amine (intermediate **146b**, 11.97 g, 90 mmol), HATU (46.6 g, 123 mmol) and *N,N*-diisopropylethylamine (49 mL, 284 mmol) in DMF (150 mL) was stirred at rt for 18 h. The mixture was diluted with EtOAc, washed 2 times with water and 2 times with 10% K₂CO₃ in water. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give 3-(benzyloxy)-4-oxo-N-(1-vinylcyclobutyl)-4H-pyran-2-carboxamide (intermediate **146c**, 25.6 g), used as such in the next step.

Synthesis of intermediate 146d:

A mixture of 3-(benzyloxy)-4-oxo-N-(1-vinylcyclobutyl)-4H-pyran-2-carboxamide (intermediate **146c**, 25.6 g, 78.681 mmol) in NH₃ (28% in water) (133 mL) and dioxane (250 mL) was stirred at rt for 6 h. The mixture was diluted with water and acidified with HCl 3N. The mixture was extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (irregular 20-45 µm, 330 g, CH₂Cl₂/CH₃OH 99/1 to 93/7) to give 3-(benzyloxy)-4-oxo-N-(1-vinylcyclobutyl)-1,4-dihydropyridine-2-carboxamide (intermediate **146d**, 20 g).

Synthesis of intermediate 146e:

1-amino-3-(benzyloxy)-4-oxo-N-(1-vinylcyclobutyl)-1,4-dihydropyridine-2-carboxamide (intermediate **146e**, 14.9 g) was obtained using the procedure described for intermediate **1b**. It was purified by trituration in EtOAc and washed with diisopropylether.

Synthesis of intermediate 146f:

1-amino-3-(benzyloxy)-4-oxo-N-(1-vinylcyclobutyl)-1,4-dihydropyridine-2-carboxamide (intermediate **146e**, 9.5 g, 27.991 mmol) was suspended in EtOH (133 mL). The mixture was heated at 100°C, then paraformaldehyde (0.84 g, 27.991 mmol) was added. The reaction mixture was heated at 120°C for 1h45 min. The solvent was

concentrated under reduced pressure, a few mL of EtOH were added and white solid was filtered and dried under vacuum pressure to give a first batch of 5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **146f**, 6.2g). Mother layers (5.6 g) were evaporated and then purified by flash column chromatography on silica gel (120 g, eluent DCM/MeOH 94:6 to 90:10) to give, after solidification in EtOH/diisopropylether, a second batch of intermediate **146f** (1.3 g).

Synthesis of intermediate **146g**:

5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **146f**, 20 g, 56.914 mmol) was dissolved under N₂ atmosphere in dry DMF (200 mL). The reaction mixture was cooled down to -10° C, then NaH (60% in oil) (2.5 g, 62.606 mmol) was added. After stirring 10 min at -10°C, a solution of 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene (intermediate **74c**, 20.2 g, 68.297 mmol) in dry DMF (100 mL) was added dropwise and the reaction mixture was stirred between -10 and 0°C during 1h. The solution was diluted with EtOAc (1000 mL) and washed twice with a saturated aqueous solution of NH₄Cl (2 x 500 mL), once with water (500 mL) and once with brine (500 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification was carried out by flash column chromatography on silica gel (220 g, eluent DCM/MeOH 100:0 - 98:2 - 90:10) to give 1-((2-(allyloxy)-3,4-difluorophenyl)(phenyl)methyl)-5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **146g**, 17.6 g).

Synthesis of intermediate **146h**:

In a 2 L flask, a solution of 1-((2-(allyloxy)-3,4-difluorophenyl)(phenyl)methyl)-5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **146g**, 8.45 g, 13.86 mmol) in dry dichloroethane (1100 mL) was degassed under N₂ for 1 h. Hoveyda-Grubbs II catalyst (1.74 g, 2.772 mmol) in solution in 50 mL of dichloroethane was added dropwise over 4 h (12.5 mL/hour) at 100°C. The reaction was then stirred at 100°C for 2 h under nitrogen atmosphere. The reaction medium was allowed to cool to room temperature and 18 g of SiliaMetS[®] DMT were added and the mixture was stirred overnight. A few MeOH was added to the mixture, which was then filtered over a pad of celite[®] and washed with solution of CH₂Cl₂/MeOH (90/10). Solvent was concentrated in vacuo. The resulting crude brown oil was purified by flash chromatography on silica gel (120 g, eluent CH₂Cl₂/MeOH 99.5:0.5 / 98:2 / 90:10) to give, after crystallization in CH₃CN/diisopropylether, (E)-12'-(benzyloxy)-3',4'-difluoro-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-

[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (intermediate **146h**, 3.28 g).

Different batches of **146h** were combined (13.5 g). A purification was performed via achiral SFC (Stationary phase: AMINO 5 μ m 150*30 mm, Mobile phase: 87% CO₂, 13% MeOH) yielding 11.99 g.

The enantiomers were separated via chiral SFC (Stationary phase: Chiralpak IG 5 μ m 250*30mm, Mobile phase: 55% CO₂, 45% of a mixture of MeOH/CH₂Cl₂ 90/10) to afford the first eluted enantiomer **146ha** (5.18 g) and the second eluted enantiomer **146hb** (5.22 g).

Synthesis of compound **146A**:

TFA (33.2 mL, 438.352 mmol) was added to enantiomer **146ha** (5.05 g; 8.769 mmol). The mixture was stirred at rt for 1h and then concentrated under reduced pressure. The residue was purified by preparative LC (regular SiOH 30 μ m, 120 g, CH₂Cl₂/MeOH from 99:1 to 97:3) to give, after crystallization in Et₂O, (18'R,E)-3',4'-difluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (compound **146A**, 3.27 g).

Compound **146A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.95 (br t, *J*=6.5 Hz, 1 H) 7.40 - 7.50 (m, 1 H) 7.33 (br d, *J*=7.3 Hz, 1 H) 7.13 - 7.24 (m, 3 H) 7.09 (br s, 2 H) 6.52 (br d, *J*=14.8 Hz, 1 H) 6.09 - 6.27 (m, 1 H) 5.49 (d, *J*=7.9 Hz, 1 H) 5.24 (s, 1 H) 5.11 (br d, *J*=13.6 Hz, 1 H) 4.82 (br t, *J*=9.5 Hz, 1 H) 4.47 - 4.62 (m, 1 H) 3.84 (br d, *J*=13.6 Hz, 1 H) 2.86 (q, *J*=10.3 Hz, 1 H) 2.43 - 2.46 (m, 1 H) 2.01 - 2.16 (m, 2 H) 1.71 - 1.81 (m, 1 H) 1.54 - 1.67 (m, 1 H)

LC/MS (method LC-C): Rt 3.06 min, MH⁺ 492

$[\alpha]_D^{20}$: -688.89 ° (c 0.099, DMF)

Chiral HPLC (method HPLC-A): Rt 11.11 min, chiral purity 100%

Synthesis of compound **146B**:

(18'S,E)-3',4'-difluoro-12'-hydroxy-18'-phenyl-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (compound **146B**) was obtained using the procedure described for compound **146A**.

Compound **146B**:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.95 (br t, *J*=6.8 Hz, 1 H) 7.40 - 7.52 (m, 1 H) 7.35 (br d, *J*=7.5 Hz, 1 H) 7.14 - 7.20 (m, 3 H) 7.09 (br s, 2 H) 6.53 (br d, *J*=15.3 Hz, 1 H) 6.11 - 6.26 (m, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.24 (s, 1 H) 5.11 (d, *J*=13.7 Hz, 1 H) 4.82 (br t, *J*=9.7 Hz, 1 H) 4.48 - 4.61 (m, 1 H) 3.84 (d, *J*=13.7 Hz, 1 H) 2.80 - 2.90 (m,

¹H) 2.41 - 2.46 (m, 1 H) 2.01 - 2.17 (m, 2 H) 1.75 (q, *J*=9.2 Hz, 1 H) 1.52 - 1.67 (m, 1 H)

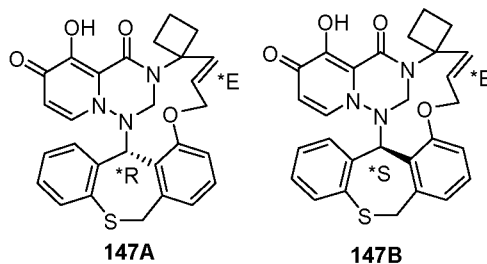
LC/MS (method LC-C): Rt 3.02 min, MH⁺ 492

[α]_D²⁰: +651.10 ° (c 0.182, DMF)

5 Chiral HPLC (method HPLC-A): Rt 6.07 min, chiral purity 100%

Example 147: synthesis of (17a'*R,*E)-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9'-

10 [3,4](epirop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **147A**), (17a'*S,*E)-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9'-[3,4](epirop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **147B**).



15

Compounds **147A** and **147B** were synthesized according to the procedures described in example **46** starting from intermediate **146f** and **37c**.

20 **Compound 147A:**

LC/MS (method LC-C): Rt 2.98 min, MH⁺ 500

[α]_D²⁰: +500.53 ° (c 0.188, DMF)

Chiral HPLC (method HPLC-B): Rt 6.47 min, chiral purity 100%

25 **Compound 147B:**

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.12 - 11.64 (m, 1 H) 7.43 (d, *J*=7.6 Hz, 1 H) 7.37 - 7.42 (m, 1 H) 7.28 (d, *J*=7.8 Hz, 1 H) 7.16 (d, *J*=7.2 Hz, 1 H) 7.05 - 7.11 (m, 1 H) 6.98 - 7.03 (m, 1 H) 6.80 - 6.87 (m, 1 H) 6.70 (d, *J*=7.2 Hz, 1 H) 6.43 (d, *J*=15.7 Hz, 1 H) 6.13 (dt, *J*=15.3, 7.5 Hz, 1 H) 5.86 (d, *J*=13.4 Hz, 1 H) 5.61 (d, *J*=7.7 Hz, 1 H) 5.42 (s, 1 H) 5.14 (d, *J*=13.6 Hz, 1 H) 4.73 - 4.80 (m, 1 H) 4.64 - 4.72 (m, 1 H) 3.86 (t, *J*=12.7 Hz, 2 H) 2.76 - 2.87 (m, 1 H) 2.41 - 2.47 (m, 1 H) 1.97 - 2.16 (m, 2 H) 1.74 (q, *J*=9.7 Hz, 1 H) 1.53 - 1.68 (m, 1 H)

LC/MS (method LC-C): Rt 2.98 min, MH⁺ 500

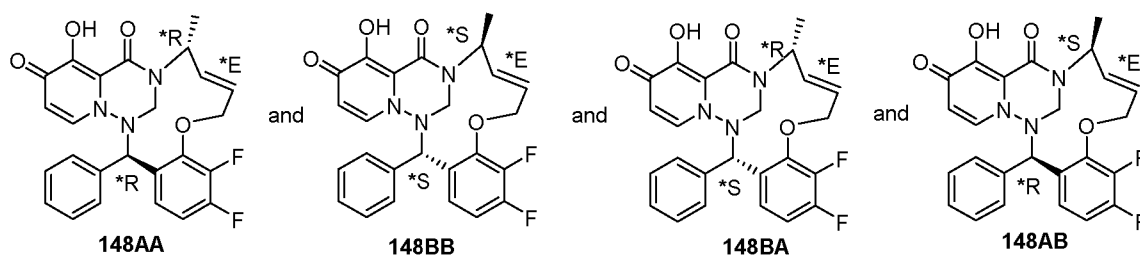
[α]_D²⁰: -511.54 ° (c 0.13, DMF)

30

Chiral HPLC (method HPLC-B): Rt 7.31 min, chiral purity 100%

Example 148: synthesis of (9*R,18*R,*E)-3,4-difluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

- 5 f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **148AA**) and (9*S,18*S,*E)-3,4-difluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **148BB**) and (9*R,18*S,*E)-3,4-difluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-
- 10 f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **148BA**) and (9*S,18*R,*E)-3,4-difluoro-12-hydroxy-9-methyl-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **148AB**)



Compounds **148AA**, **148BB**, **148BA** and **148AB** were synthesized according to the procedures described in example **29** starting from intermediate **74c**.

Compound 148AA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.95 (br t, *J*=6.9 Hz, 1 H) 7.45 - 7.55 (m, 1 H) 7.03 - 7.29 (m, 6 H) 6.35 (ddd, *J*=15.5, 10.0, 5.0 Hz, 1 H) 5.68 (br d, *J*=10.1 Hz, 1 H) 5.48 (d, *J*=7.6 Hz, 1 H) 5.40 - 5.46 (m, 1 H) 5.15 (s, 1 H) 5.04 (d, *J*=13.6 Hz, 1 H) 4.92 (br dd, *J*=11.3, 5.4 Hz, 1 H) 4.26 (d, *J*=13.6 Hz, 1 H) 4.09 (br t, *J*=10.6 Hz, 1 H) 1.16 (d, *J*=6.9 Hz, 3 H)

LC/MS (method LC-C): Rt 2.83 min, MH⁺ 466

[α]_D²⁰: -570.00° (c 0.07, DMF)

Chiral HPLC (method HPLC-B): Rt 4.60 min, chiral purity 100%

Compound 148AB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.00 (br t, *J*=7.1 Hz, 1 H) 7.44 - 7.53 (m, 1 H) 7.34 (d, *J*=7.6 Hz, 1 H) 7.17 (br d, *J*=3.2 Hz, 3 H) 7.08 (br s, 2 H) 6.43 - 6.61 (m, 1 H) 5.88 - 6.06 (m, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.35 (s, 1 H) 5.18 (d, *J*=14.2 Hz, 1 H) 4.70

(br t, $J=10.2$ Hz, 1 H) 4.57 (br dd, $J=9.8, 5.0$ Hz, 1 H) 4.22 (d, $J=14.2$ Hz, 1 H) 3.70 (br dd, $J=9.6, 7.1$ Hz, 1 H) 1.76 (d, $J=6.9$ Hz, 3 H)

LC/MS (method LC-C): Rt 2.87 min, MH^+ 466

$[\alpha]_D^{20}$: -713.25 ° (c 0.083, DMF)

5 Chiral HPLC (method HPLC-A): Rt 8.38 min, chiral purity 100%

Compound 148BA:

LC/MS (method LC-C): Rt 2.87 min, MH^+ 466

$[\alpha]_D^{20}$: +700.00 ° (c 0.068, DMF)

10 Chiral HPLC (method HPLC-A): Rt 4.31 min, chiral purity 100%

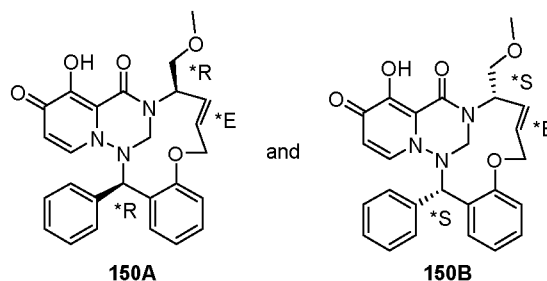
Compound 148BB:

LC/MS (method LC-C): Rt 2.83 min, MH^+ 466

$[\alpha]_D^{20}$: +560.2 ° (c 0.098, DMF)

15 Chiral HPLC (method HPLC-B): Rt 4.42 min, chiral purity 99.59%

Example 150: synthesis of (9*R,18*R,*E)-12-hydroxy-9-(methoxymethyl)-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **150A**), (9*S,18*S,*E)-12-hydroxy-9-(methoxymethyl)-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **150B**)



Compounds **150A** and **150B** were synthesized according to the procedures described in example **39** starting from intermediate 5-(benzyloxy)-3-(1-methoxybut-3-en-2-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized as **39e** from 1-methoxy-3-buten-2-amine [CAS 1391253-55-6]).

Compound 150A:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.01 (dd, $J=7.9, 1.3$ Hz, 1 H) 7.33 - 7.41 (m, 1 H) 7.27 - 7.32 (m, 1 H) 7.03 - 7.19 (m, 7 H) 6.29 (ddd, $J=15.4, 10.1, 5.0$ Hz, 1 H) 5.32 -

5.45 (m, 3 H) 5.16 (s, 1 H) 4.91 (d, $J=13.9$ Hz, 1 H) 4.82 (dd, $J=11.3, 5.4$ Hz, 1 H) 4.22 (d, $J=13.6$ Hz, 1 H) 4.02 (t, $J=10.9$ Hz, 1 H) 3.35 - 3.39 (m, 2 H) 3.14 (s, 3 H)

LC/MS (method LC-C): Rt 2.66 min, MH^+ 460

$[\alpha]_D^{20}$: -555.23 ° (c 0.172, DMF)

5 Chiral HPLC (method HPLC-B): Rt 6.14 min, chiral purity 100%

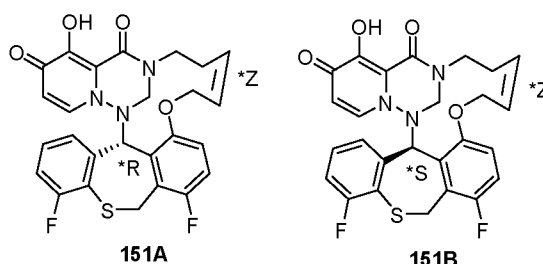
Compound 150B:

LC/MS (method LC-C): Rt 2.66 min, MH^+ 460

$[\alpha]_D^{20}$: +526.29 ° (c 0.194, DMF)

10 Chiral HPLC (method HPLC-B): Rt 11.76 min, chiral purity 100%

Example 151: synthesis of (1*R,13*Z)-20,25-difluoro-7-hydroxy-16-oxa-23-thia-2,3,10-triazahexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione (Compound **151A**) and
 15 (1*S,13*Z)-20,25-difluoro-7-hydroxy-16-oxa-23-thia-2,3,10-triazahexacyclo[15.12.1.12,10.03,8.021,30.024,29]hentriaconta-4,7,13,17,19,21(30),24(29),25,27-nonaene-6,9-dione (Compound **151B**)



20

Compounds **151A** and **151B** were synthesized according to the procedures described in example **88** starting from intermediate 10-(allyloxy)-11-chloro-4,7-difluoro-6,11-dihydrodibenzo[b,e]thiepine (synthesized as **88n** from 5-fluoro-2-hydroxy-benzoic acid [CAS 345-16-4] and 2-fluoro-benzenethiol [CAS 2557-78-0]).

25

Compound 151A:

LC/MS (method LC-C): Rt 2.89 min, MH^+ 510

$[\alpha]_D^{20}$: +150.50° (c 0.200, DMF)

30

Compound 151B:

^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 11.28 - 12.22 (m, 1 H) 7.35 (t, $J=9.1$ Hz, 1 H) 7.23 (d, $J=7.7$ Hz, 1 H) 7.07 - 7.18 (m, 2 H) 6.91 (td, $J=7.9, 5.9$ Hz, 1 H) 6.49 (d, $J=7.7$ Hz, 1 H) 6.13 (s, 1 H) 6.02 - 6.11 (m, 1 H) 5.91 - 6.01 (m, 1 H) 5.57 - 5.67 (m, 2 H)

4.96 (d, $J=13.4$ Hz, 1 H) 4.46 - 4.59 (m, 2 H) 4.40 (d, $J=13.4$ Hz, 1 H) 4.19 - 4.30 (m, 1 H) 4.14 (d, $J=14.1$ Hz, 1 H) 2.78 - 2.89 (m, 1 H) 2.11 - 2.31 (m, 2 H)

LC/MS (method LC-C): Rt 2.89 min, MH^+ 510

$[\alpha]_D^{20}$: -155.8 ° (c 0.181, DMF)

5

Example 152: synthesis of (9*S,18*S,*E)-9-cyclopropyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **152AA**) and

(9*R,18*R,*E)-9-cyclopropyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-

10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

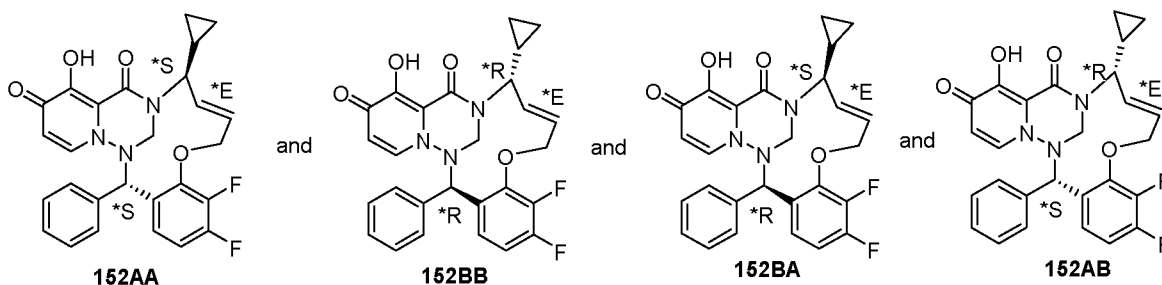
(Compound **152BB**) and (9*S,18*R,*E)-9-cyclopropyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **152BA**) and

(9*R,18*S,*E)-9-cyclopropyl-3,4-difluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-

15 10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **152AB**)



20 Compounds **152AA**, **152BB**, **152BA** and **152AB** were synthesized according to the procedures described in example **39** starting from intermediates 3-(1-cyclopropylallyl)-5-(benzyloxy)-3-(1-cyclopropylallyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized from cyclopropane-methane-amine [CAS 1160786-80-8] and **74c**).

25 **Compound 152AA:**

LC/MS (method LC-C): Rt 3.04 min, MH^+ 492

$[\alpha]_D^{20}$: +575.71 ° (c 0.07, DMF)

Chiral HPLC (method HPLC-A): Rt 5.15 min, chiral purity 100%

30 **Compound 152AB:**

LC/MS (method LC-C): Rt 3.03 min, MH^+ 492

$[\alpha]_D^{20}$: +575.00° (c 0.056, DMF)

Chiral HPLC (method HPLC-B): Rt 4.57 min, chiral purity 100%

Compound 152BA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.95 (br t, *J*=6.8 Hz, 1 H) 7.43 - 7.55 (m, 1 H)
7.03 - 7.32 (m, 6 H) 6.32 (ddd, *J*=15.6, 10.1, 5.5 Hz, 1 H) 5.82 (br dd, *J*=15.8, 6.6 Hz, 1 H)
5 H 5.48 (d, *J*=7.6 Hz, 1 H) 5.11 - 5.19 (m, 2 H) 4.91 (dd, *J*=11.3, 5.4 Hz, 1 H) 4.60 (dd,
J=9.5, 6.6 Hz, 1 H) 4.40 (d, *J*=13.6 Hz, 1 H) 4.12 (br t, *J*=10.7 Hz, 1 H) 1.05 - 1.14 (m,
1 H) 0.49 - 0.57 (m, 1 H) 0.45 (tt, *J*=8.6, 4.5 Hz, 1 H) 0.33 (dq, *J*=9.3, 4.7 Hz, 1 H)
0.23 (dq, *J*=9.5, 4.9 Hz, 1 H)

LC/MS (method LC-C): Rt 3.03 min, MH⁺ 492

10 [α]_D²⁰: -544.44 ° (c 0.072, DMF)

Chiral HPLC (method HPLC-B): Rt 7.57 min, chiral purity 100%

Compound 152BB:

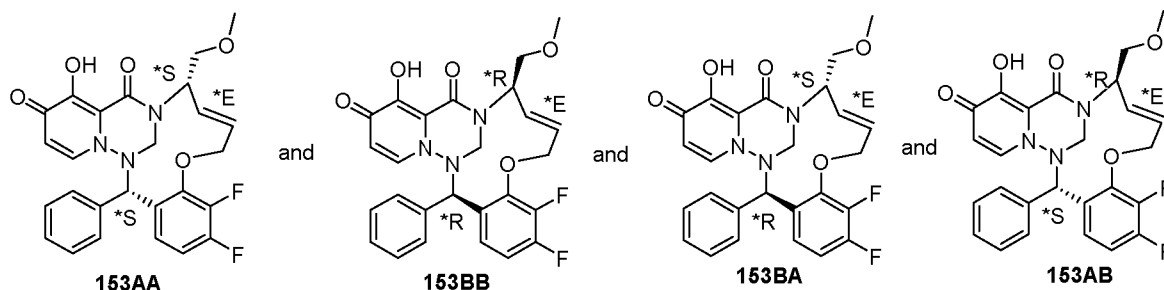
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 (br t, *J*=6.9 Hz, 1 H) 7.40 - 7.53 (m, 1 H)
15 7.31 (d, *J*=7.6 Hz, 1 H) 6.95 - 7.27 (m, 5 H) 6.61 (br dd, *J*=13.6, 10.4 Hz, 1 H) 5.77 -
5.96 (m, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.35 (s, 1 H) 5.20 (d, *J*=13.9 Hz, 1 H) 4.71 (br t,
J=10.4 Hz, 1 H) 4.58 (br dd, *J*=10.4, 5.4 Hz, 1 H) 4.12 (d, *J*=13.9 Hz, 1 H) 2.73 (t,
J=9.8 Hz, 1 H) 2.04 - 2.17 (m, 1 H) 0.50 - 0.66 (m, 2 H) 0.28 (br dd, *J*=9.1, 4.1 Hz, 1
H) 0.10 (br dd, *J*=9.0, 3.9 Hz, 1 H)

20 LC/MS (method LC-C): Rt 3.04 min, MH⁺ 492

[α]_D²⁰: -543.48 ° (c 0.069, DMF)

Chiral HPLC (method HPLC-A): Rt 6.68 min, chiral purity 100%

Example 153: synthesis of (9*S,18*S,*E)-3,4-difluoro-12-hydroxy-9-(methoxymethyl)-
25 18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-
f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **153AA**) and
(9*R,18*R,*E)-3,4-difluoro-12-hydroxy-9-(methoxymethyl)-18-phenyl-6,9-dihydro-
18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **153BB**) and (9*S,18*R,*E)-3,4-difluoro-12-hydroxy-9-(methoxymethyl)-
30 18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-
f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **153BA**) and
(9*R,18*S,*E)-3,4-difluoro-12-hydroxy-9-(methoxymethyl)-18-phenyl-6,9-dihydro-
18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
(Compound **153AB**)



Compounds **153AA**, **153BB**, **153BA** and **153AB** were synthesized according to the procedures described in example **150** starting from **74c**.

Compound 153AA:

LC/MS (method LC-C): Rt 2.83 min, MH^+ 496

$[\alpha]_D^{20}$: +515.79 ° (c 0.076, DMF)

Chiral HPLC (method HPLC-B): Rt 11.97 min, chiral purity 100%

Compound 153AB:

LC/MS (method LC-C): Rt 2.77 min, MH^+ 496

$[\alpha]_D^{20}$: +551.56 ° (c 0.064, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 153BA:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.98 (br t, $J=7.3$ Hz, 1 H) 7.42 - 7.54 (m, 1 H) 7.33 (d, $J=7.6$ Hz, 1 H) 6.92 - 7.28 (m, 5 H) 6.35 - 6.56 (m, 1 H) 5.96 - 6.17 (m, 1 H) 5.50 (d, $J=7.6$ Hz, 1 H) 5.35 (s, 1 H) 5.19 (d, $J=13.9$ Hz, 1 H) 4.71 (br t, $J=10.2$ Hz, 1 H) 4.56 (br dd, $J=10.2, 5.2$ Hz, 1 H) 4.30 (d, $J=13.9$ Hz, 1 H) 4.11 - 4.19 (m, 1 H) 4.03 - 4.10 (m, 1 H) 3.77 (dt, $J=9.1, 6.9$ Hz, 1 H) 3.27 (s, 3 H)

LC/MS (method LC-C): Rt 2.77 min, MH^+ 496

$[\alpha]_D^{20}$: -698.25 ° (c 0.057, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 153BB:

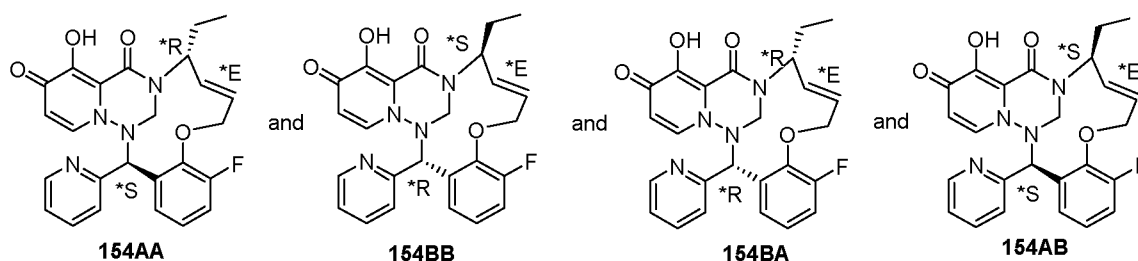
^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.94 (br t, $J=6.9$ Hz, 1 H) 7.44 - 7.54 (m, 1 H) 7.02 - 7.34 (m, 6 H) 6.44 (ddd, $J=15.4, 10.4, 5.0$ Hz, 1 H) 5.72 (dd, $J=15.8, 6.6$ Hz, 1 H) 5.44 - 5.55 (m, 2 H) 5.17 (s, 1 H) 5.00 (d, $J=13.6$ Hz, 1 H) 4.94 (dd, $J=11.2, 5.2$ Hz, 1 H) 4.31 (d, $J=13.6$ Hz, 1 H) 4.09 (br t, $J=10.9$ Hz, 1 H) 3.42 - 3.50 (m, 2 H) 3.23 (s, 3 H)

LC/MS (method LC-C): Rt 2.83 min, MH^+ 496

$[\alpha]_D^{20}$: -526.15 ° (c 0.065, DMF)

Chiral HPLC (method HPLC-B): Rt 6.44 min, chiral purity 100%

Example 154: synthesis of (9*R,18*S,*E)-9-ethyl-4-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **154AA**) and (9*S,18*R,*E)-9-ethyl-4-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **154BB**) and (9*R,18*R,*E)-9-ethyl-4-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **154BA**) and (9*S,18*S,*E)-9-ethyl-4-fluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **154AB**)



Compounds **154AA**, **154BB**, **154BA** and **154AB** were synthesized according to the procedures described in example **39** starting from intermediate 2-(2-(allyloxy)-3-fluorophenyl)(chloromethyl-pyridine) (synthesized as **41b** from 2-bromopyridine [CAS 109-04-6] and 3-fluoro-2-(2-propen-1-yloxy)benzaldehyde [CAS 1106304-54-4]).

Compound 154AA:

LC/MS (method LC-C): Rt 2.63 min, MH^+ 463

$[\alpha]_D^{20}$: +651.32 ° (c 0.076, DMF)

Chiral HPLC (method HPLC-A): Rt 5.32 min, chiral purity 100%

Compound 154AB:

LC/MS (method LC-C): Rt 2.57 min, MH^+ 463

$[\alpha]_D^{20}$: +627.16 ° (c 0.081, DMF)

Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 154BA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.38 (d, *J*=4.2 Hz, 1 H) 7.95 (br d, *J*=7.3 Hz, 1 H) 7.64 (td, *J*=7.6, 1.2 Hz, 1 H) 7.32 - 7.44 (m, 2 H) 7.28 (d, *J*=7.7 Hz, 1 H) 7.22 (dd, *J*=7.2, 5.0 Hz, 1 H) 7.11 (d, *J*=7.7 Hz, 1 H) 6.35 (ddd, *J*=15.5, 10.3, 5.1 Hz, 1 H) 5.56 (br dd, *J*=15.7, 6.4 Hz, 1 H) 5.50 (d, *J*=7.7 Hz, 1 H) 5.41 (s, 1 H) 5.17 (q, *J*=7.3 Hz, 1 H) 5.07 (d, *J*=13.6 Hz, 1 H) 4.88 (dd, *J*=11.4, 5.3 Hz, 1 H) 4.23 (d, *J*=13.6 Hz, 1 H) 4.02 (br t, *J*=10.9 Hz, 1 H) 1.38 - 1.63 (m, 2 H) 0.83 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 2.57 min, MH⁺ 463

[α]_D²⁰: -596.92 ° (c 0.13, DMF)

10 Chiral HPLC (method HPLC-A and B): **No separation observed**

Compound 154BB:

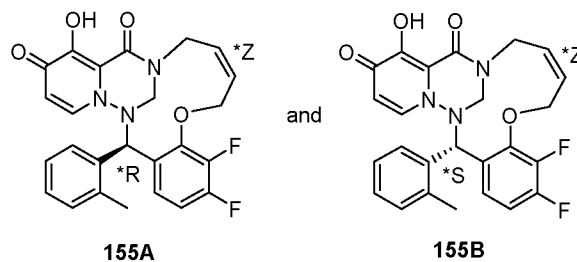
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.31 - 8.39 (m, 1 H) 7.98 (d, *J*=7.3 Hz, 1 H) 7.62 (td, *J*=7.7, 1.7 Hz, 1 H) 7.28 - 7.44 (m, 2 H) 7.14 - 7.23 (m, 3 H) 6.41 (br dd, *J*=15.0, 10.0 Hz, 1 H) 5.78 - 6.00 (m, 1 H) 5.62 (s, 1 H) 5.50 (d, *J*=7.6 Hz, 1 H) 5.21 (d, *J*=13.9 Hz, 1 H) 4.60 - 4.69 (m, 1 H) 4.49 - 4.59 (m, 1 H) 4.23 (d, *J*=14.1 Hz, 1 H) 3.41 - 3.53 (m, 1 H) 2.26 - 2.41 (m, 1 H) 2.08 - 2.23 (m, 1 H) 0.87 (t, *J*=7.4 Hz, 3 H)

LC/MS (method LC-C): Rt 2.63 min, MH⁺ 463

[α]_D²⁰: -681.25 ° (c 0.08, DMF)

20 Chiral HPLC (method HPLC-A): Rt 6.25 min, chiral purity 100%

Example 155: synthesis (18^{*}R,^{*}Z)-3,4-difluoro-12-hydroxy-18-(*o*-tolyl)-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **155A**) and (18^{*}S,^{*}Z)-3,4-difluoro-12-hydroxy-18-(*o*-tolyl)-6,9-dihydro-18H-10,17-methanobenzo[*b*]pyrido[1,2-*f*][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **155B**)



30 Compounds **155A** and **155B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(*o*-tolyl)methyl)-3,4-difluorobenzene (synthesized as **74c** from 1-bromo-2-methyl-benzene [CAS 95-46-5]).

Compound 155A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 (br t, *J*=6.3 Hz, 1 H) 7.41 - 7.55 (m, 2 H) 7.30 (br d, *J*=6.6 Hz, 1 H) 7.03 - 7.14 (m, 2 H) 6.95 - 7.02 (m, 1 H) 6.16 - 6.32 (m, 1 H) 5.93 - 6.13 (m, 1 H) 5.64 (br s, 1 H) 5.52 (d, *J*=7.9 Hz, 1 H) 5.16 (d, *J*=13.9 Hz, 1 H) 4.88 - 4.95 (m, 1 H) 4.84 (br dd, *J*=13.7, 4.6 Hz, 1 H) 4.27 - 4.38 (m, 2 H) 3.24 (br dd, *J*=13.9, 8.2 Hz, 1 H) 2.23 (s, 3 H)

LC/MS (method LC-C): Rt 2.79 min, MH⁺ 466

[α]_D²⁰: -670.33 ° (c 0.091, DMF)

Chiral HPLC (method HPLC-A): Rt 5.03 min, chiral purity 100%

Compound 155B:

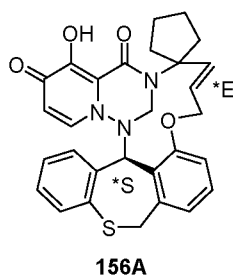
LC/MS (method LC-C): Rt 2.79 min, MH⁺ 466

[α]_D²⁰: +682.89 ° (c 0.076, DMF)

Chiral HPLC (method HPLC-A): Rt 5.75 min, chiral purity 100%

Example 156: synthesis of (17a'*S,*E)-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclopentane-1,9'-

[3,4](epi prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **156A**)



Compound **156A** was synthesized according to the procedures described in example **46** starting from intermediate 5-(benzyloxy)-3-(1-vinylcyclopentyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized as **146f** from 1-ethenylcyclopentanamine [CAS 1391303-96-0]).

Compound 156A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.36 - 7.43 (m, 2 H) 7.23 (d, *J*=7.6 Hz, 1 H) 7.18 (d, *J*=7.3 Hz, 1 H) 7.06 - 7.11 (m, 1 H) 6.99 - 7.03 (m, 1 H) 6.84 (td, *J*=7.5, 1.1 Hz, 1 H) 6.71 - 6.76 (m, 1 H) 6.22 (dt, *J*=15.5, 7.5 Hz, 1 H) 6.04 - 6.14 (m, 1 H) 5.84 (d, *J*=13.2 Hz, 1 H) 5.61 (d, *J*=7.6 Hz, 1 H) 5.44 (s, 1 H) 5.13 (d, *J*=13.6 Hz, 1 H) 4.79 (dd, *J*=11.0, 7.3 Hz, 1 H) 4.53 (dd, *J*=11.2, 7.4 Hz, 1 H) 4.20 (d, *J*=13.6 Hz, 1 H) 3.85

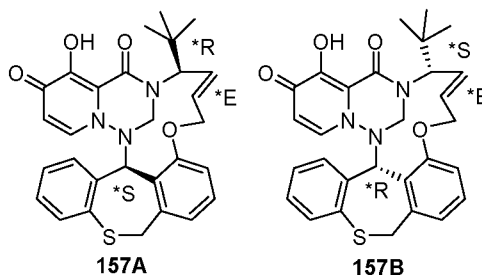
(d, $J=13.2$ Hz, 1 H) 2.74 - 2.81 (m, 1 H) 2.34 - 2.38 (m, 1 H) 1.76 - 1.84 (m, 1 H) 1.68 - 1.75 (m, 1 H) 1.52 - 1.67 (m, 2 H) 1.32 - 1.52 (m, 2 H)

LC/MS (method LC-C): Rt 3.14 min, MH^+ 514

$[\alpha]_D^{20}$: -473.93 ° (c 0.171, DMF)

5 Chiral HPLC (method HPLC-B): Rt 7.41 min, chiral purity 100%

Example 157: synthesis of (9*R,17a*S,*E)-9-(tert-butyl)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **157A**),
 10 (9*S,17a*R,*E)-9-(tert-butyl)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **157B**).



15 Compounds **157A** and **157B** were synthesized according to the procedures described in example **46** starting from intermediate 5-(benzyloxy)-3-(4,4-dimethylpent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized as **29c** from 4,4-dimethyl-1-penten-3-amine [CAS 36024-39-2]).

Compound 157A:

^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.44 (d, $J=7.6$ Hz, 1 H) 7.35 - 7.42 (m, 1 H) 7.28 (d, $J=8.2$ Hz, 1 H) 7.16 (d, $J=7.3$ Hz, 1 H) 7.04 - 7.11 (m, 1 H) 6.97 - 7.03 (m, 1 H) 6.79 - 6.86 (m, 1 H) 6.67 (d, $J=7.3$ Hz, 1 H) 6.53 (dd, $J=15.3, 10.2$ Hz, 1 H) 5.82 - 5.94 (m, 2 H) 5.61 (d, $J=7.6$ Hz, 1 H) 5.51 (s, 1 H) 5.25 (d, $J=13.9$ Hz, 1 H) 4.74 (dd, $J=10.7, 5.0$ Hz, 1 H) 4.58 - 4.67 (m, 1 H) 4.34 (d, $J=13.9$ Hz, 1 H) 3.88 (d, $J=13.2$ Hz, 1 H) 3.34 (br d, $J=10.4$ Hz, 3 H) 1.07 (s, 9 H)

LC/MS (method LC-C): Rt 3.26 min, MH^+ 516

$[\alpha]_D^{20}$: -405.23 ° (c 0.153, DMF)

30 Chiral HPLC (method HPLC-B): Rt 4.60 min, chiral purity 100%

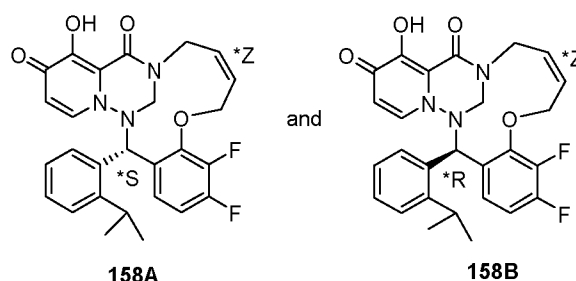
Compound 157B:

LC/MS (method LC-C): Rt 3.26 min, MH^+ 516

$[\alpha]_D^{20}$: +418.3 ° (c 0.153, DMF)

Chiral HPLC (method HPLC-B): Rt 5.39 min, chiral purity 100%

Example 158: synthesis (18*S,*Z)-3,4-difluoro-12-hydroxy-18-(2-isopropylphenyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **158A**) and (18*R,*Z)-3,4-difluoro-12-hydroxy-18-(2-isopropylphenyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (compound **158B**)



Compounds **158A** and **158B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(2-isopropylphenyl)methyl)-3,4-difluorobenzene (synthesized as **74c** from 1-bromo-1-isopropyl-benzene [CAS 7073-94-1]).

Compound **158A**:

LC/MS (method LC-C): Rt 3.01 min, MH^+ 494

$[\alpha]_D^{20}$: +627.1 ° (c 0.214, DMF)

Chiral HPLC (method HPLC-B): Rt 4.10 min, chiral purity 100%

Compound **158B**:

^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 9.86 - 11.64 (m, 1 H) 7.99 (br t, $J=6.1$ Hz, 1 H) 7.42 - 7.55 (m, 2 H) 7.22 (br d, $J=7.6$ Hz, 1 H) 7.12 - 7.19 (m, 2 H) 7.05 - 7.11 (m, 1 H) 6.18 (dt, $J=15.1, 7.4$ Hz, 1 H) 5.94 - 6.10 (m, 1 H) 5.84 (br s, 1 H) 5.49 (d, $J=7.9$ Hz, 1 H) 5.15 (d, $J=13.6$ Hz, 1 H) 4.84 (br dd, $J=13.9, 4.7$ Hz, 1 H) 4.73 - 4.81 (m, 1 H) 4.34 - 4.45 (m, 1 H) 4.31 (d, $J=13.9$ Hz, 1 H) 3.25 (br dd, $J=13.9, 8.2$ Hz, 1 H) 3.01 (dt, $J=13.3, 6.7$ Hz, 1 H) 1.18 (d, $J=6.9$ Hz, 3 H) 0.93 (d, $J=6.6$ Hz, 3 H)

LC/MS (method LC-C): Rt 3.01 min, MH^+ 494

$[\alpha]_D^{20}$: -623.63 ° (c 0.182, DMF)

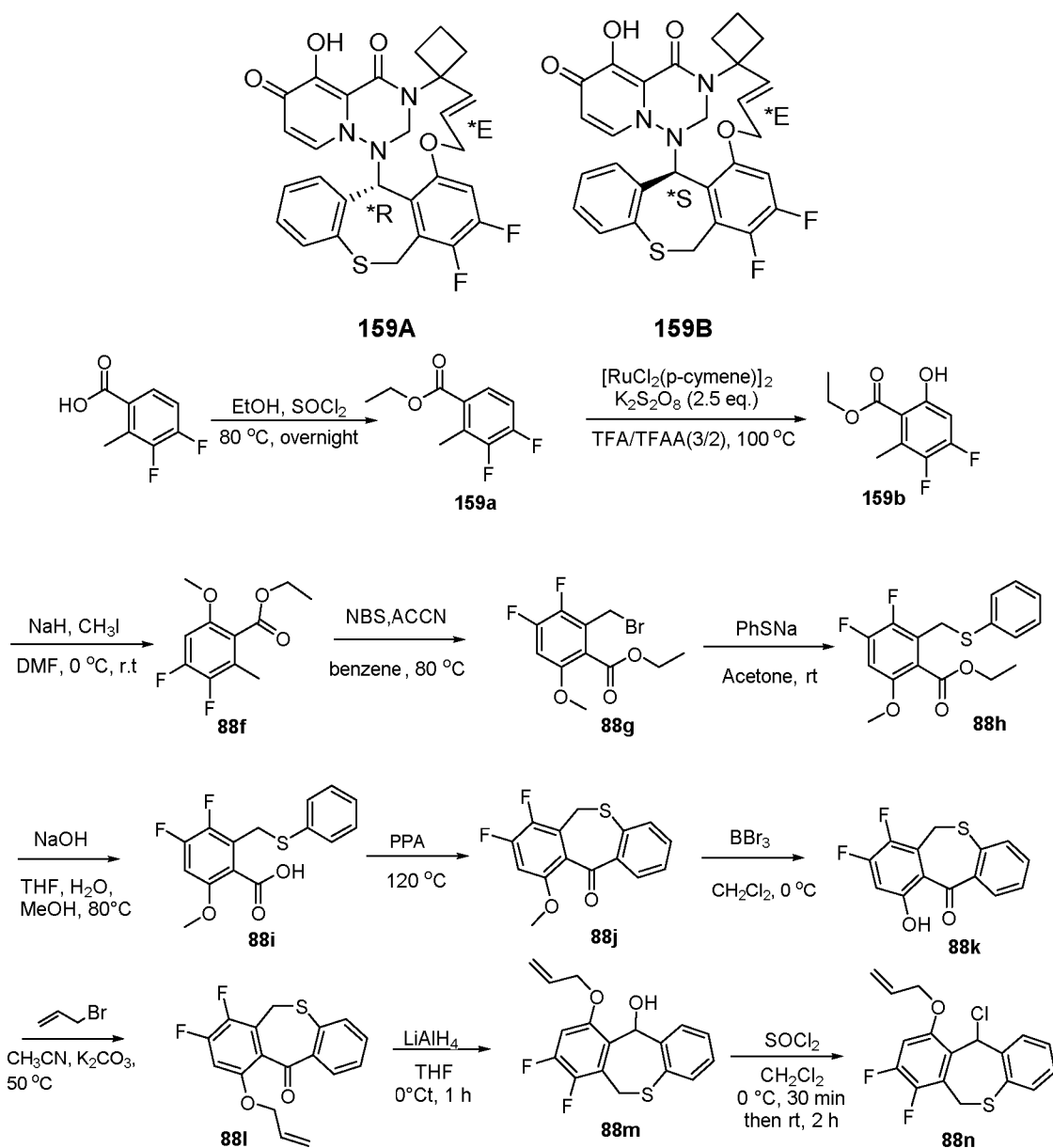
Chiral HPLC (method HPLC-B): Rt 4.49 min, chiral purity 100%

Example 159: synthesis of (17a'*R,*E)-24',25'-difluoro-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9']-

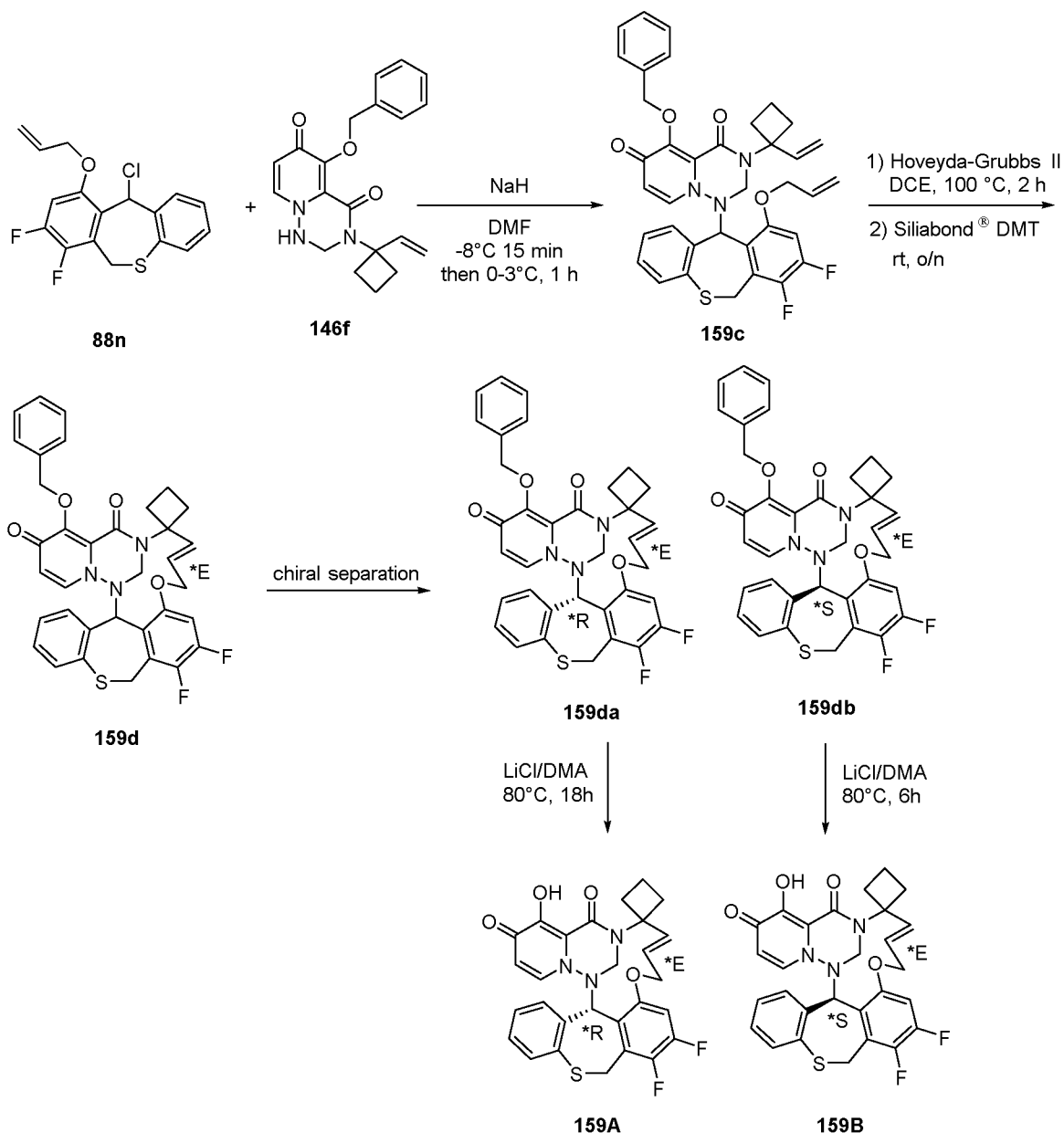
[3,4](epi-prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **159A**), (17a'*S,*E)-

5 24',25'-difluoro-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9']-

[3,4](epi-prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **159B**)



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Synthesis of intermediate 159a:

SOCl₂ (311.025 g, 2614.318 mmol) was slowly added into EtOH (1.5 L) at 0°C. Then 3,4-difluoro-2-methylbenzoic acid [CAS 157652-31-8] (150 g, 871.439 mmol) was added. The resulting mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated under vacuum. The residue obtained was adjusted to pH 8 with a saturated sodium bicarbonate solution in water and extracted by EtOAc. Then the organic layer was washed with brine and dried over Na₂SO₄. The solution was concentrated under vacuum to afford ethyl 3,4-difluoro-2-methylbenzoate (intermediate **159a**, 160 g) as a yellow oil.

Synthesis of intermediate 159b:

Into a 2000 ml three round bottom flask, ethyl 3,4-difluoro-2-methylbenzoate (160 g, 799.273 mmol) was dissolved in TFA (600 ml) and TFAA (400 ml). Then $K_2S_2O_8$ (539.509 g, 1998.182 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (48.915 g, 79.927 mmol) were added. The resulting solution was stirred 4 days at 100°C. When the reaction was completed, it was concentrated under vacuum and the residue was diluted with EtOAc, washed with H_2O and brine. Then the organic phase was concentrated under reduced pressure. The residue was purified by gel chromatography (0-5% EtOAc/petroleum ether) to afford ethyl 3,4-difluoro-6-hydroxy-2-methylbenzoate (intermediate **159b**, 100 g) as a white solid.

Synthesis of intermediate 88f:

Into a 2000 ml round bottom flask, ethyl 3,4-difluoro-6-hydroxy-2-methylbenzoate (100 g, 462.575 mmol) was dissolved in DMF (1.5 L). Then NaH (22.204 g, 555.090 mmol) was added and the solution was stirred 0.5 h at 0°C. Iodomethane (78.789 g, 555.090 mmol) was added and the reaction was stirred 1 h. When the reaction was completed, it was quenched with H_2O (1.5 L) and a solid was formed. The solution was filtrated and the solid was dissolved by EtOAc. The organic layer was washed with brine and dried over Na_2SO_4 , and then concentrated under reduced pressure. 100 g of ethyl 3,4-difluoro-6-methoxy-2-methylbenzoate (intermediate **88f**) was obtained as a yellow solid.

Synthesis of intermediate 88g:

To a solution of ethyl 3,4-difluoro-6-methoxy-2-methylbenzoate (50 g, 217.195 mmol) in benzene (1 L) was added 1-bromopyrrolidine-2,5-dione (96.643 g, 542.987 mmol), ACCN [CAS 2094-98-6] (2.65 g, 10.860 mmol). The resulting solution was stirred at 80°C for 48 h. The resulting mixture was quenched with water and concentrated under vacuum. Water was added, and the solution was extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated under vacuum. The residue was purified by gel chromatography (0-10% EtOAc/petroleum ether) to afford ethyl 2-(bromomethyl)-3,4-difluoro-6-methoxybenzoate (intermediate **88g**, 50 g) as a yellow solid.

Synthesis of intermediate 88h:

To a solution of ethyl 2-(bromomethyl)-3,4-difluoro-6-methoxybenzoate (250 g, 808.789 mmol) in acetone (1.5 L) was added sodium benzenethiolate (117.578 g, 889.668 mmol). The resulting mixture was stirred at r.t. for 3 h, then filtered and the solid was washed with acetone three times. The filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by gel chromatography

(0-15% EtOAc/petroleum ether) to afford ethyl 3,4-difluoro-6-methoxy-2-((phenylthio)methyl)benzoate (intermediate **88h**, 200 g) as a yellow solid.

Synthesis of intermediate 88i:

5 To a solution of ethyl 3,4-difluoro-6-methoxy-2-((phenylthio)methyl)benzoate (100 g, 295.535 mmol) in EtOH/H₂O (2:1) at 0°C was added sodium hydroxide (59.107 g, 1477.677 mmol). The resulting mixture was stirred at 80°C for overnight, then concentrated under reduced pressure. Water was added to the reaction solution. The pH value of the water layer was adjusted to pH ~3, then extracted with EtOAc. The organic
10 layers were combined, washed with H₂O, brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the 3,4-difluoro-6-methoxy-2-((phenylthio)methyl)benzoic acid an yellow solid (intermediate **88i**, 160g).

Synthesis of intermediate 88j:

15 3,4-difluoro-6-methoxy-2-((phenylthio)methyl)benzoic acid (43 g, 138.568 mmol) was added to the solution of polyphosphoric acid (PPA) at 80°C, then the reaction was warmed up to 120°C and stirred for 1 h. The resulting reaction mixture was cooled to 0°C, then ice-cold water was added to the reaction mixture and stirred for another 2 h. The precipitate was filtered off, washed with water and dried to obtain 7,8-difluoro-10-methoxydibenzo[b,e]thiepin-11(6H)-one (intermediate **88j**, 30 g) as a brown solid.
20

Synthesis of intermediate 88k:

To a solution of 7,8-difluoro-10-methoxydibenzo[b,e]thiepin-11(6H)-one (25 g, 85.529 mmol) in CH₂Cl₂ (0.5 L) was added dropwise tribromoborane over 1 h (170 mL, 1.0 M
25 in CH₂Cl₂) at 0°C. The mixture was stirred for another 2 h at 0°C, and was quenched with aq. sat. NaHCO₃ solution at 0°C. The resulting mixture was extracted with CH₂Cl₂ and the organic layers were combined, washed with H₂O and brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford 7,8-difluoro-10-hydroxydibenzo[b,e]thiepin-11(6H)-one (intermediate **88k**, 20 g) as a yellow solid.
30

Synthesis of intermediate 88l:

To a solution of 7,8-difluoro-10-hydroxydibenzo[b,e]thiepin-11(6H)-one (22 g, 71.872 mmol) in CH₃CN (0.5 L) was added potassium carbonate (29.755 g, 215.615 mmol) and 3-bromoprop-1-ene (9.564 g, 79.059 mmol). The resulting mixture was heated at 50°C
35 for 3 h. The reaction mixture was filtered, the solid was washed with EtOAc three times, then the filtrate was dried over anhydrous sodium sulfate and concentrated. The residue was washed with EtOAc/hexane to afford 10-(allyloxy)-7,8-difluorodibenzo[b,e]thiepin-11(6H)-one as an yellow solid (intermediate **88l**, 22g).

Synthesis of intermediate 88m:

To a solution of 10-(allyloxy)-7,8-difluorodibenzo[b,e]thiepin-11(6H)-one (26 g, 81.674 mmol) in THF (500 mL) was added LiAlH₄ (3.104 g, 81.674 mmol) at 0°C under N₂.
5 After 1 h at 0°C, the resulting mixture was quenched with water (4 mL), then aqueous NaOH solution (15%, 4 mL) and water (12 mL) were added. The resulting mixture was filtered on celite® and the solid was washed with EtOAc three times. The filtrate was washed with H₂O, dried over anhydrous sodium sulfate and concentrated. The residue was washed with EtOAc/hexane (10/1). Then the resulting solution was filtered to afford
10 10-(allyloxy)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-ol (intermediate **88m**, 20 g) as an off-white solid.

Synthesis of intermediate 88n:

At 0°C, SOCl₂ (5.2 mL, 71.303 mmol) was added dropwise to a solution of 10-(allyloxy)-
15 7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-ol (19.12 g, 59.419 mmol) in CH₂Cl₂ (285 mL). The mixture was stirred at 0°C for 30 min then at rt for 2 h. The mixture was evaporated until dryness, taken up with toluene and evaporated again to give 10-(allyloxy)-11-chloro-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepine (intermediate **88n**), used as such in the next step.

Synthesis of intermediate 159c:

5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (20 g, 49.516 mmol) was dissolved in dry DMF (280 mL) under N₂ atmosphere, and the solution was cooled to -9°C. NaH (60% in oil) (2.38 g, 59.419 mmol) was added
25 and the reaction mixture was stirred at -8°C for 15 min. 10-(allyloxy)-11-chloro-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepine (20.13 g, 59.419 mmol) in DMF (100 mL) was added dropwise (over 30 mins) at -8°C. The brine/ice cooling bath was changed for an ice bath and the reaction was stirred at 0-3°C for 1 h. The reaction was quenched with cold water (300 mL) and EtOAc was added (500 mL). The reaction mixture was stirred
30 at rt for 1 h and the precipitate was filtered off, washed with EtOAc (200 mL) and dried to give a first batch of 1-(10-(allyloxy)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl)-5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (intermediate **159c**, 25.7 g). The filtrate was extracted with EtOAc. The organic layer was washed with water and brine, dried over MgSO₄, filtered
35 and the solvent was evaporated. The residue was purified via preparative LC (Stationary phase: irregular SiOH 40 µm, Mobile phase: 99% CH₂Cl₂, 1% MeOH) to give a second batch of intermediate **159c** (5.8 g).

Synthesis of intermediate 159d:

The solvent was degassed by bubbling N₂ through for 1 h.

Using a syringe pump, a solution of Hoveyda-Grubbs II catalyst (1.21 g, 1.927 mmol) in dichloroethane (30 mL) was added dropwise over 2 h to a solution of 1-(10-(allyloxy)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl)-5-(benzyloxy)-3-(1-vinylcyclobutyl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (12.6 g, 19.27 mmol) in dichloroethane (1230 mL) under N₂ bubbling through the mixture at 100°C. The reaction was monitored 15 min after the end of the addition (LC/MS showed the reaction was completed). The mixture was cooled to rt and SiliaMetS[®] DMT (12.6 g, 7.71 mmol) was added and the reaction mixture was stirred at rt overnight. The mixture was filtered through a pad of celite[®]. The celite[®] was washed with CH₂Cl₂/CH₃OH 95/5 (200 mL) and the filtrate was concentrated under reduced pressure (m = 11.8 g). This batch was combined with other batches before purification (total amount 34 g). The combined batch was taken up with 150 mL of CH₃CN and stirred for 30 min at rt. The precipitate was filtered off and dried (m = 24.1 g). This batch was combined with another one to afford 30.8 g of (*E)-12'-(benzyloxy)-24',25'-difluoro-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9'-[3,4](epi)prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepine[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (intermediate **159d**). The enantiomers were separated via chiral SFC (Stationary phase: CHIRACEL OJ-H 5 µm 250 x 30 mm, Mobile phase: 70% CO₂, 30% MeOH (0.3% iPrNH₂)) to afford the first eluted enantiomer **159da** (16.5 g) and the second eluted enantiomer **159db** (15.1 g).

Synthesis of compound 159A:

LiCl (257 mg, 6.057 mmol) was added to a solution of enantiomer **159da** (379 mg, 0.606 mmol) in DMA (5.6 mL) and the mixture was stirred at 80°C for 18 h. The mixture was cooled to rt and ice with HCl 0.5N was added. The mixture was extracted with CH₂Cl₂. The organic layer was washed with HCl 0.5N (3 times), dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. CH₂Cl₂ was added, the white solid was filtered and dried under vacuum pressure at 60° C overnight to give enantiomer **159A** (197 mg).

Synthesis of compound 159B:

Enantiomer **159db** (19.5 g, 31.16 mmol) and LiCl (13.2 g, 311.65 mmol) in DMA (246 mL) was stirred at 80°C for 6 h. The mixture was cooled to rt and diluted with water. The mixture was extracted with CH₂Cl₂ (2 times). The organic layer was washed with water, dried over MgSO₄, filtered and the solvent was evaporated. Purification was carried out by flash chromatography over silica gel (330 g SiO₂ 30 µm

(CH₂Cl₂/CH₃OH/AcOH 99/1/0 to 90/10/0.5)) The pure fractions were collected and evaporated to dryness to give compound **159B** (16.5 g). This batch was combined with another one to afford 19.6 g. 50 mL of CH₃CN was added. The mixture was stirred at rt for 2 h. The precipitate was filtered off and dried (m = 11.8 g).

5

Compound 159A:LC/MS (method LC-C): Rt 3.16 min, MH⁺ 536[α]_D²⁰: +489.23 ° (c 0.13, DMF)

Chiral HPLC (method HPLC-B): Rt 5.99 min, chiral purity 100%

10

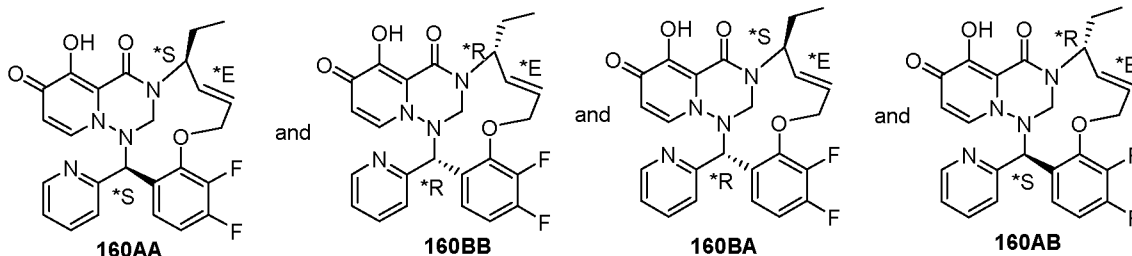
Compound 159B:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.00 (br d, *J*=2.4 Hz, 1 H) 7.55 (dd, *J*=11.9, 7.5 Hz, 1 H) 7.40 (d, *J*=7.6 Hz, 1 H) 7.07 - 7.18 (m, 1 H) 7.00 - 7.06 (m, 1 H) 6.86 (td, *J*=7.4, 1.2 Hz, 1 H) 6.65 - 6.74 (m, 1 H) 6.48 (d, *J*=15.6 Hz, 1 H) 6.11 - 6.26 (m, 1 H) 5.75 (dd, *J*=14.0, 2.3 Hz, 1 H) 5.61 (d, *J*=7.7 Hz, 1 H) 5.37 (s, 1 H) 5.11 (d, *J*=13.8 Hz, 1 H) 4.63 - 4.85 (m, 2 H) 3.89 - 4.19 (m, 2 H) 2.71 - 2.87 (m, 1 H) 2.40 - 2.46 (m, 1 H) 2.01 - 2.22 (m, 2 H) 1.69 - 1.81 (m, 1 H) 1.52 - 1.68 (m, 1 H)

LC/MS (method LC-C): Rt 3.16 min, MH⁺ 536[α]_D²⁰: -502.15 ° (c 0.093, DMF)

20 Chiral HPLC (method HPLC-B): Rt 6.70 min, chiral purity 100%

Example 160: synthesis of (9*S,18*S,*E)-9-ethyl-3,4-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **160AA**) and (9*R,18*R,*E)-9-ethyl-3,4-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **160BB**) and (9*S,18*R,*E)-9-ethyl-3,4-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **160BA**) and (9*R,18*S,*E)-9-ethyl-3,4-difluoro-12-hydroxy-18-(pyridin-2-yl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **160AB**)



Compounds **160AA**, **160BB**, **160BA** and **160AB** were synthesized according to the procedures described in example **39** starting from intermediate 2-((2-(allyloxy)-3,4-difluorophenyl)chloromethyl)pyridine (synthesized as **45b** from 2-bromopyridine [CAS 109-04-6] and **74a**).

Compound 160AA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.39 (d, *J*=3.8 Hz, 1 H) 7.89 - 8.01 (m, 1 H) 7.64 (td, *J*=7.7, 1.7 Hz, 1 H) 7.41 - 7.55 (m, 1 H) 7.18 - 7.33 (m, 2 H) 7.09 (d, *J*=7.7 Hz, 1 H) 6.36 (ddd, *J*=15.6, 10.1, 5.2 Hz, 1 H) 5.71 (br dd, *J*=15.7, 6.5 Hz, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.36 (s, 1 H) 5.16 (q, *J*=7.6 Hz, 1 H) 5.05 (d, *J*=13.6 Hz, 1 H) 4.93 (dd, *J*=11.4, 5.4 Hz, 1 H) 4.24 (d, *J*=13.6 Hz, 1 H) 4.10 (br t, *J*=10.8 Hz, 1 H) 1.38 - 1.64 (m, 2 H) 0.83 (t, *J*=7.3 Hz, 3 H)
LC/MS (method LC-C): Rt 2.71 min, MH⁺ 481
[α]_D²⁰: -476.71 ° (c 0.146, DMF)
Chiral HPLC (method HPLC-A and B): No separation observed

Compound 160AB:

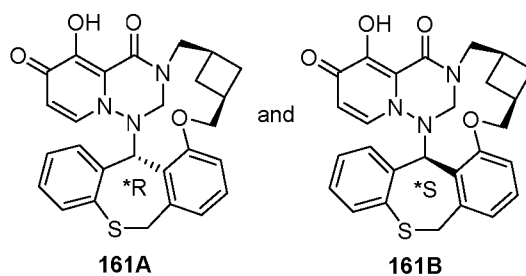
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.36 (d, *J*=3.8 Hz, 1 H) 7.99 (br t, *J*=6.8 Hz, 1 H) 7.62 (td, *J*=7.6, 1.7 Hz, 1 H) 7.41 - 7.51 (m, 1 H) 7.18 - 7.22 (m, 1 H) 7.16 (dd, *J*=7.9, 3.2 Hz, 2 H) 6.44 (br dd, *J*=15.3, 9.9 Hz, 1 H) 5.97 (ddd, *J*=15.1, 9.4, 5.8 Hz, 1 H) 5.54 (s, 1 H) 5.49 (d, *J*=7.9 Hz, 1 H) 5.20 (d, *J*=13.9 Hz, 1 H) 4.66 - 4.76 (m, 1 H) 4.60 (br dd, *J*=10.6, 5.5 Hz, 1 H) 4.23 (d, *J*=13.9 Hz, 1 H) 3.39 - 3.48 (m, 1 H) 2.28 - 2.35 (m, 1 H) 2.10 - 2.22 (m, 1 H) 0.87 (t, *J*=7.4 Hz, 3 H)
LC/MS (method LC-C): Rt 2.77 min, MH⁺ 481
[α]_D²⁰: -548.99 ° (c 0.149, DMF)
Chiral HPLC (method HPLC-A): Rt 5.93 min, chiral purity 100%

Compound 160BA:

LC/MS (method LC-C): Rt 2.77 min, MH⁺ 481
[α]_D²⁰: +524.41 ° (c 0.127, DMF)
Chiral HPLC (method HPLC-A): Rt 4.75 min, chiral purity 100%

Compound 160BB:

LC/MS (method LC-C): Rt 2.71 min, MH⁺ 481
[α]_D²⁰: +512.18 ° (c 0.156, DMF)
Chiral HPLC (method HPLC-A and B): No separation observed

Example 161: Synthesis of Compound 161A and Compound 161B

Compounds **161A** and **161B** were synthesized according to the procedures described in example **87** starting from intermediate (3-(((tert-butyl-diphenylsilyl)oxy)methyl)cyclobutyl)methanamine (synthesized as **87e** from cis-1,3-cyclobutane-dimethanol [CAS 2453-47-6]).

Compound 161A:

LC/MS (method LC-C): Rt 2.92 min, MH⁺ 488

[α]_D²⁰: +214.62 ° (c 0.171, DMF)

Chiral HPLC (method HPLC-B): Rt 5.67 min, chiral purity 100%

Compound 161B:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.93 - 12.40 (m, 1 H) 7.31 (d, *J*=7.6 Hz, 1 H) 7.25 (t, *J*=8.0 Hz, 1 H) 7.02 - 7.10 (m, 2 H) 6.97 - 7.01 (m, 1 H) 6.94 (d, *J*=7.6 Hz, 1 H) 6.76 - 6.83 (m, 1 H) 6.70 - 6.75 (m, 1 H) 6.37 (s, 1 H) 5.76 (d, *J*=13.2 Hz, 1 H) 5.51 (d, *J*=7.9 Hz, 1 H) 5.08 (d, *J*=13.2 Hz, 1 H) 4.53 (br d, *J*=12.9 Hz, 1 H) 4.37 (d, *J*=13.2 Hz, 1 H) 3.72 - 3.90 (m, 3 H) 2.60 (br d, *J*=14.5 Hz, 1 H) 2.45 - 2.54 (m, 2 H) 2.26 - 2.36 (m, 1 H) 1.93 - 2.05 (m, 1 H) 1.61 - 1.73 (m, 1 H) 1.42 (q, *J*=10.6 Hz, 1 H)

LC/MS (method LC-C): Rt 2.92 min, MH⁺ 488

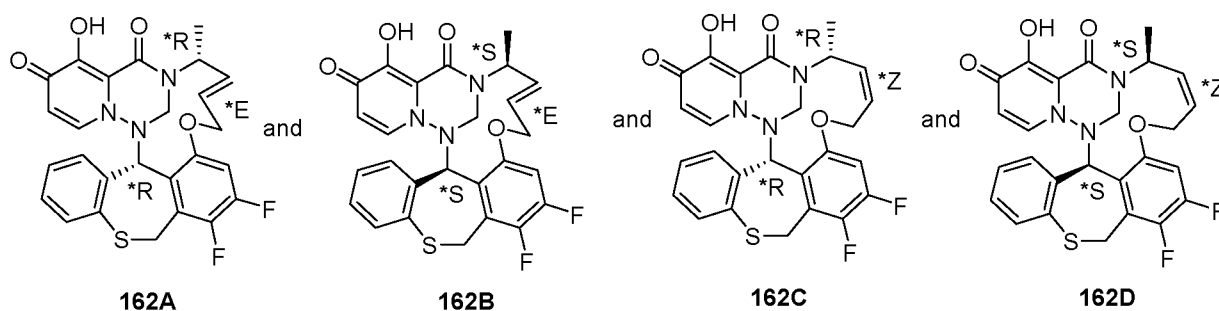
[α]_D²⁰: -217.5 ° (c 0.200, DMF)

Chiral HPLC (method HPLC-B): Rt 8.86 min, chiral purity 100%

Example 162: synthesis of (9*R,17a*R,*E)-24,25-difluoro-12-hydroxy-9-methyl-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiipino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **162A**) and (9*S,17a*S,*E)-24,25-difluoro-12-hydroxy-9-methyl-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiipino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **162B**) and (13*R,21a*R,*Z)-24,25-difluoro-16-hydroxy-13-methyl-6,10,13,21a-tetrahydro-7,8-(epiprop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiipino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-

dione (Compound **162C**) and (13*S,21a*S,*Z)-24,25-difluoro-16-hydroxy-13-methyl-6,10,13,21a-tetrahydro-7,8-(epi prop[1]en[1]yl[3]ylidene)-14,21-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-15,17-dione (Compound **162D**)

5



Compounds **162A**, **162B**, **16C** and **162D** were synthesized according to the procedures described in example **159** starting from intermediate **29c** and **88n**.

10

Compound **162A**:

LC/MS (method LC-C): Rt 2.98 min, MH⁺ 510

[α]_D²⁰: +459.62 ° (c 0.104, DMF)

Chiral HPLC (method HPLC-B): Rt 5.57 min, chiral purity 100%

15

Compound **162B**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.42 (dd, *J*=11.7, 7.3 Hz, 1 H) 7.27 (d, *J*=7.9 Hz, 1 H) 7.11 - 7.18 (m, 1 H) 7.04 - 7.10 (m, 1 H) 6.85 - 6.91 (m, 1 H) 6.78 - 6.84 (m, 1 H) 6.30 (ddd, *J*=15.5, 9.7, 6.0 Hz, 1 H) 5.65 - 5.76 (m, 2 H) 5.60 (d, *J*=7.9 Hz, 1 H) 5.42 (quin, *J*=6.9 Hz, 1 H) 5.27 (s, 1 H) 5.02 (d, *J*=13.9 Hz, 1 H) 4.85 (dd, *J*=11.3, 5.7 Hz, 1 H) 4.44 (d, *J*=13.9 Hz, 1 H) 4.32 (t, *J*=10.7 Hz, 1 H) 4.11 (d, *J*=13.9 Hz, 1 H) 1.18 (d, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 2.98 min, MH⁺ 510

[α]_D²⁰: -460.71 ° (c 0.084, DMF)

Chiral HPLC (method HPLC-B): Rt 8.26 min, chiral purity 100%

Compound **162C**:

LC/MS (method LC-C): Rt 3.07 min, MH⁺ 510

[α]_D²⁰: +130.69 ° (c 0.101, DMF)

Chiral HPLC (method HPLC-B): Rt 4.32 min, chiral purity 100%

30

Compound 162D:

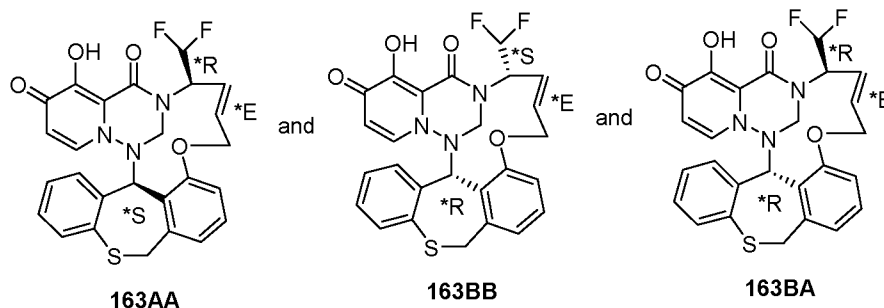
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.39 (br dd, *J*=11.7, 6.9 Hz, 1 H) 7.14 - 7.27 (m, 3 H) 6.89 (br t, *J*=7.1 Hz, 1 H) 6.49 - 6.65 (m, 2 H) 6.21 (dt, *J*=10.3, 6.7 Hz, 1 H) 6.05 (s, 1 H) 5.59 - 5.75 (m, 2 H) 5.22 (br d, *J*=13.2 Hz, 1 H) 4.83 (br dd, *J*=10.2, 7.1 Hz, 1 H) 4.41 - 4.59 (m, 2 H) 4.04 - 4.20 (m, 2 H) 1.44 (br d, *J*=6.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.07 min, MH⁺ 510

[α]_D²⁰: -131.07 ° (c 0.103, DMF)

Chiral HPLC (method HPLC-B): Rt 8.10 min, chiral purity 99.28%

- 10 **Example 163:** synthesis of (9*R,17a*S,*E)-9-(difluoromethyl)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi)prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **163AA**) and (9*S,17a*R,*E)-9-(difluoromethyl)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi)prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **163BB**) and (9*R,17a*R,*E)-9-(difluoromethyl)-12-hydroxy-2,6,9,17a-tetrahydro-3,4-(epi)prop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **163BA**)



Compounds **163AA**, **163BB** and **163BA** were synthesized according to the procedures described in example 37 starting from intermediate 3-(1,1-difluorobut-3-en-2-yl)-5-benzyloxy-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (synthesized as **39e** from 1,1-difluoro-3-buten-2-amine,HCl [CAS 2061940-62-1]).

Compound 163AA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (br t, *J*=7.6 Hz, 1 H) 7.30 (br d, *J*=7.5 Hz, 1 H) 7.17 (br s, 4 H) 6.86 (br t, *J*=6.5 Hz, 1 H) 6.24 - 6.74 (m, 4 H) 6.11 (s, 1 H) 5.61 - 5.83 (m, 2 H) 5.20 (br d, *J*=13.2 Hz, 1 H) 4.81 - 4.97 (m, 1 H) 4.58 (br d, *J*=12.7 Hz, 3 H) 3.86 (br d, *J*=13.4 Hz, 1 H)

LC/MS (method LC-C): Rt 2.90 min, MH⁺ 510

$[\alpha]_D^{20}$: -179.52 ° (c 0.083, DMF)

Chiral HPLC (method HPLC-B): Rt 7.69 min, chiral purity 100%

Compound 163BB:

5 LC/MS (method LC-C): Rt 2.82 min, MH⁺ 510

$[\alpha]_D^{20}$: +433.33 ° (c 0.090, DMF)

Chiral HPLC (method HPLC-B): Rt 5.27 min, chiral purity 100%

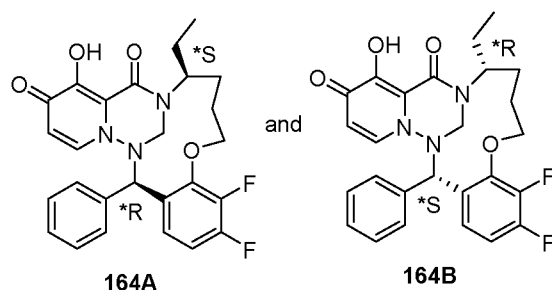
Compound 163BA:

10 LC/MS (method LC-C): Rt 2.89 min, MH⁺ 510

$[\alpha]_D^{20}$: +230.56 ° (c 0.108, DMF)

Chiral HPLC: No chiral HPLC performed.

Example 164: synthesis of (9*S,18*R)-9-ethyl-3,4-difluoro-12-hydroxy-18-phenyl-
 15 6,7,8,9-tetrahydro-18H-10,17-methanobenzo[b]pyrido[1,2-
 f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **164A**) and (9*R,18*S)-9-
 ethyl-3,4-difluoro-12-hydroxy-18-phenyl-6,7,8,9-tetrahydro-18H-10,17-
 methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione
 (Compound **164B**)



Compounds **164A** and **164B** were synthesized according to the procedures described in
 example **80** starting from intermediates 6-((tert-butyldiphenylsilyl)oxy)hexan-3-amine
 and 2-(allyloxy)-1-(chloro(phenyl)methyl)-3,4-difluorobenzene (synthesized as **80h**
 25 from 1,4-hexanediol [CAS 16432-53-4]).

Compound 164A:

LC/MS (method LC-C): Rt 3.07 min, MH⁺ 482

$[\alpha]_D^{20}$: +263.82 ° (c 0.152, DMF)

30 Chiral HPLC (method HPLC-B): Rt 4.22 min, chiral purity 100%

Compound 164B:

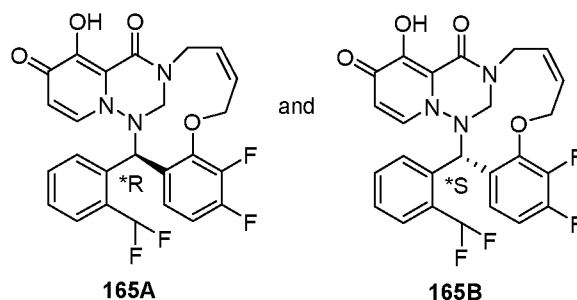
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.41 - 12.26 (m, 1 H) 7.87 (br t, *J*=6.8 Hz, 1 H) 7.36 - 7.46 (m, 1 H) 7.11 - 7.35 (m, 6 H) 5.78 (s, 1 H) 5.51 (d, *J*=7.6 Hz, 1 H) 4.97 (d, *J*=13.6 Hz, 1 H) 4.50 (br dd, *J*=12.1, 2.7 Hz, 1 H) 4.29 - 4.44 (m, 2 H) 4.05 (br t, *J*=11.5 Hz, 1 H) 1.99 - 2.12 (m, 1 H) 1.83 - 1.95 (m, 1 H) 1.65 (dt, *J*=14.3, 10.2 Hz, 1 H) 1.26 - 1.42 (m, 2 H) 0.89 - 1.03 (m, 1 H) 0.77 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.07 min, MH⁺ 482

[α]_D²⁰: -233.73 ° (c 0.166, DMF)

Chiral HPLC (method HPLC-B): Rt 6.85 min, chiral purity 96.00%

Example 165: synthesis of (18*R,Z)-18-(2-(difluoromethyl)phenyl)-3,4-difluoro-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **165A**) and (18*S,*Z)-18-(2-(difluoromethyl)phenyl)-3,4-difluoro-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **165B**)



Compounds **165A** and **165B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(2-(difluoromethyl)phenyl)methyl)-3,4-difluorobenzene (synthesized as **70a** from 1-bromo-2-(difluoromethyl)benzene [CAS 845866-82-2]).

Compound 165A:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.98 - 8.07 (m, 1 H) 7.95 (br d, *J*=7.9 Hz, 1 H) 7.46 - 7.57 (m, 2 H) 7.34 - 7.45 (m, 3 H) 6.96 - 7.27 (m, 1 H) 6.14 - 6.31 (m, 1 H) 5.95 - 6.10 (m, 1 H) 5.44 - 5.64 (m, 2 H) 5.20 (d, *J*=13.9 Hz, 1 H) 4.95 - 5.06 (m, 1 H) 4.82 (br dd, *J*=13.9, 4.1 Hz, 1 H) 4.36 (br d, *J*=13.9 Hz, 2 H) 3.22 (br dd, *J*=13.9, 7.9 Hz, 1 H)

LC/MS (method LC-C): Rt 2.77 min, MH⁺ 502

[α]_D²⁰: -570.37 ° (c 0.270, DMF)

Chiral HPLC (method HPLC-A): Rt 4.49 min, chiral purity 100%

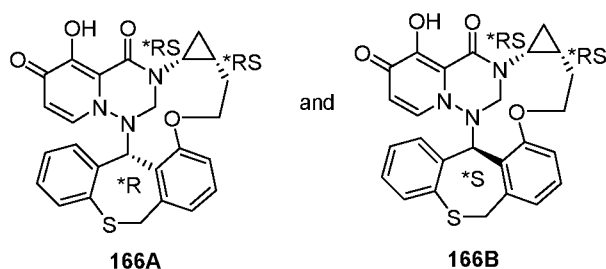
Compound 165B:LC/MS (method LC-C): Rt 2.77 min, MH⁺ 502[α]_D²⁰: +576.14 ° (c 0.197, DMF)

5 Chiral HPLC (method HPLC-A): Rt 5.23 min, chiral purity 100%

Example 166: synthesis of cis-(11a*RS,12a*RS,13S,20a*R)-15-hydroxy-6,11,11a,12,12a,20a-hexahydro-10H-7,8-(epiprop[1]en[1]yl[3]ylidene)-13,20-

10 f[1]oxa[5,6,9]triazacyclotridecine-14,16-dione (Compound **166A**) and cis-(11a*RS,12a*RS,13S,20a*S)-15-hydroxy-6,11,11a,12,12a,20a-hexahydro-10H-7,8-(epiprop[1]en[1]yl[3]ylidene)-13,20-methanobenzo[6,7]thiepino[4,5-

15 c[cyclopropa[j]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-14,16-dione (Compound **166B**)



Compounds **166A** and **166B** were synthesized according to the procedures described in example **87** starting from intermediate cis-(1*RS,2*RS)-2-(2-((tert-butyl

20 butyldiphenylsilyl)oxy)ethyl)cyclopropan-1-amine (synthesized as described for 2-[2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-cyclopropanamine [CAS 134716-76-0] but using tert-butyl-diphenylchlorosilane as a protecting group),

Compound 166A:25 LC/MS (method LC-C): Rt 2.82 min, MH⁺ 474[α]_D²⁰: +188.70 ° (c 0.177, DMF)

Chiral HPLC (method HPLC-B): Rt 7.28 min, chiral purity 100%

Compound 166B:

30 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.64 (t, *J*=7.9 Hz, 1 H) 7.33 - 7.44 (m, 2 H) 7.29 (d, *J*=7.5 Hz, 2 H) 7.23 (d, *J*=7.6 Hz, 1 H) 7.01 - 7.10 (m, 1 H) 6.85 (d, *J*=7.3 Hz, 1 H) 6.34 (s, 1 H) 5.86 (d, *J*=7.6 Hz, 1 H) 5.78 (d, *J*=13.6 Hz, 1 H) 5.31 (d, *J*=12.8 Hz, 1 H) 4.63 (br dd, *J*=11.1, 3.9 Hz, 1 H) 4.27 - 4.42 (m, 2 H) 4.02 (d, *J*=13.6 Hz, 1 H) 2.83 -

2.97 (m, 1 H) 2.51 - 2.63 (m, 1 H) 2.30 - 2.46 (m, 1 H) 1.71 - 1.85 (m, 1 H) 0.83 - 0.96 (m, 1 H) -0.02 (q, $J=6.0$ Hz, 1 H)

LC/MS (method LC-C): Rt 2.82 min, MH⁺ 474

$[\alpha]_D^{20}$: -190.23 ° (c 0.133, DMF)

5 Chiral HPLC (method HPLC-B): Rt 11.85 min, chiral purity 100%

Example 167: synthesis of (9*S,18*R,E)-9-ethyl-3,4-difluoro-12-hydroxy-18-(o-tolyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **167AA**) and (9*R,18*S,E)-

10 9-ethyl-3,4-difluoro-12-hydroxy-18-(o-tolyl)-6,9-dihydro-18H-10,17-

methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

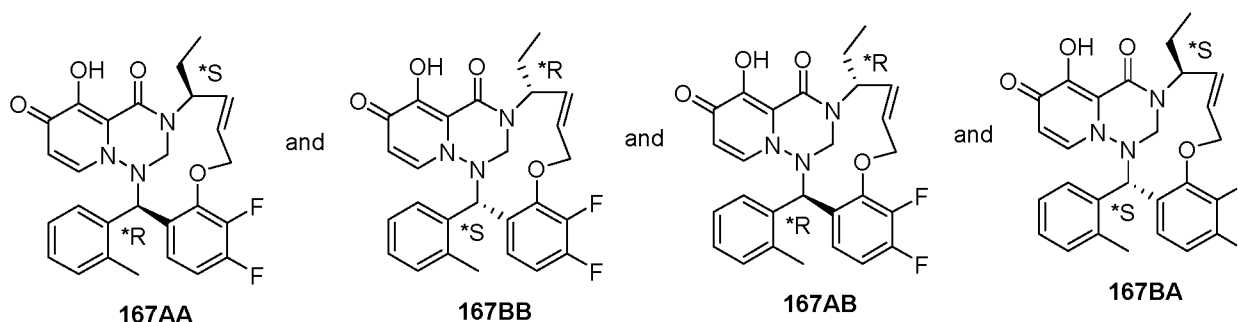
(Compound **167BB**) and (9*R,18*R,E)-9-ethyl-3,4-difluoro-12-hydroxy-18-(o-tolyl)-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **167AB**) and (9*S,18*S,E)-

15 9-ethyl-3,4-difluoro-12-hydroxy-18-(o-tolyl)-6,9-dihydro-18H-10,17-

methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **167BA**)



20

Compounds **167AA**, **167BB**, **167AB** and **167BA** were synthesized according to the procedures described in example **39** starting from intermediate 2-(allyloxy)-1-(chloro(o-tolyl)methyl)-3,4-difluorobenzene (see example **155**).

25 **Compound 167AA:**

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 (br t, $J=7.1$ Hz, 1 H) 7.42 - 7.58 (m, 2 H) 7.31 (d, $J=7.6$ Hz, 1 H) 7.03 - 7.14 (m, 2 H) 6.96 - 7.02 (m, 1 H) 6.33 (ddd, $J=15.6$, 10.1, 5.5 Hz, 1 H) 5.69 (br dd, $J=15.6$, 6.5 Hz, 1 H) 5.57 (s, 1 H) 5.51 (d, $J=7.9$ Hz, 1 H) 5.20 (q, $J=7.6$ Hz, 1 H) 5.07 (d, $J=13.6$ Hz, 1 H) 4.99 (dd, $J=11.3$, 5.4 Hz, 1 H) 4.28 (d, $J=13.6$ Hz, 1 H) 4.11 (br t, $J=10.9$ Hz, 1 H) 2.21 (s, 3 H) 1.42 - 1.63 (m, 2 H) 0.84 (t, $J=7.3$ Hz, 3 H)

30

LC/MS (method LC-C): Rt 3.11 min, MH⁺ 494

$[\alpha]_D^{20}$: -621.77 ° (c 0.147, DMF)

Chiral HPLC (method HPLC-B): Rt 5.51 min, chiral purity 100%

Compound 167BB:

5 LC/MS (method LC-C): Rt 3.10 min, MH+ 494

$[\alpha]_D^{20}$: +568.49 ° (c 0.146, DMF)

Chiral HPLC (method HPLC-B): Rt 4.85 min, chiral purity 100%

Compound 167AB:

10 ^1H NMR (500 MHz, DMSO- d_6) δ ppm 7.85 - 8.01 (m, 1 H) 7.30 - 7.50 (m, 3 H) 6.84 - 7.08 (m, 3 H) 6.28 - 6.47 (m, 1 H) 5.80 - 5.97 (m, 1 H) 5.72 (br s, 1 H) 5.45 (br d, $J=7.6$ Hz, 1 H) 5.16 (br d, $J=13.9$ Hz, 1 H) 4.68 (br t, $J=10.1$ Hz, 1 H) 4.50 - 4.61 (m, 1 H) 4.19 (br d, $J=13.9$ Hz, 1 H) 3.36 - 3.46 (m, 1 H) 2.17 - 2.33 (m, 4 H) 2.03 - 2.12 (m, 1 H) 0.80 (br t, $J=7.3$ Hz, 3 H)

15 LC/MS (method LC-C): Rt 3.18 min, MH+ 494

$[\alpha]_D^{20}$: -604.35 ° (c 0.161, DMF)

Chiral HPLC (method HPLC-A): Rt 3.97 min, chiral purity 100%

Compound 167BA:

20 LC/MS (method LC-C): Rt 3.18 min, MH+ 494

$[\alpha]_D^{20}$: +641.61 ° (c 0.149, DMF)

Chiral HPLC (method HPLC-A): Rt 4.54 min, chiral purity 100%

Example 168: synthesis of (21a'*R,*E)-24',25'-difluoro-16'-hydroxy-6',21a'-dihydro-

25 10'H-spiro[cyclobutane-1,13'-

[7,8](epirop[1]en[1]yl[3]ylidene)[14,21]methanopyrido[1,2-

f]pyrido[2',3':6,7]thiepino[4,5-c][1]oxa[5,6,9]triazacyclotridecine]-15',17'-dione

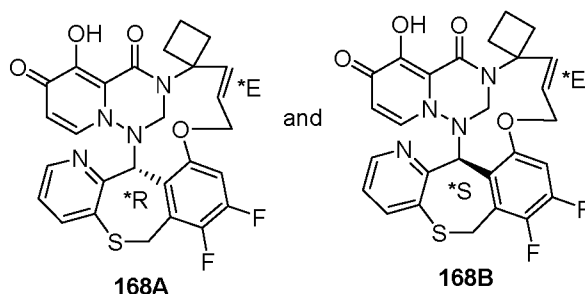
(Compound **168A**) and (21a'*S,*E)-24',25'-difluoro-16'-hydroxy-6',21a'-dihydro-10'H-

spiro[cyclobutane-1,13'-[7,8](epirop[1]en[1]yl[3]ylidene)[14,21]methanopyrido[1,2-

30 f]pyrido[2',3':6,7]thiepino[4,5-c][1]oxa[5,6,9]triazacyclotridecine]-15',17'-dione

(Compound **168B**)

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Compounds **168A** and **168B** were synthesized according to the procedures described in example **159** starting from intermediate 10-(allyloxy)-11-chloro-7,8-difluoro-6,11-dihydrobenzo[5,6]thiepino[3,2-b]pyridine (synthesized as **88n** from 3-pyridinethiol [CAS 16133-26-9]).

Compound **168A**:

LC/MS (method LC-C): Rt 2.79 min, MH⁺ 537

[α]_D²⁰: +482.67 ° (c 0.075, DMF)

Chiral HPLC (method HPLC-B): Rt 6.13 min, chiral purity 100%

Compound **168B**:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.99 (d, *J*=3.7 Hz, 1 H) 7.58 (br dd, *J*=11.8, 7.4 Hz, 1 H) 7.49 (d, *J*=7.6 Hz, 1 H) 7.31 (d, *J*=7.7 Hz, 1 H) 7.13 (dd, *J*=8.0, 4.6 Hz, 1 H) 6.44 (d, *J*=15.7 Hz, 1 H) 6.08 - 6.22 (m, 1 H) 5.80 (br d, *J*=14.7 Hz, 1 H) 5.70 (s, 1 H) 5.60 (d, *J*=7.6 Hz, 1 H) 5.10 (d, *J*=13.8 Hz, 1 H) 4.74 (br d, *J*=7.2 Hz, 2 H) 4.14 (d, *J*=14.2 Hz, 1 H) 4.04 (br d, *J*=13.8 Hz, 1 H) 2.79 (q, *J*=10.6 Hz, 1 H) 2.41 - 2.47 (m, 1 H) 2.06 - 2.19 (m, 2 H) 1.69 - 1.83 (m, 1 H) 1.52 - 1.67 (m, 1 H)

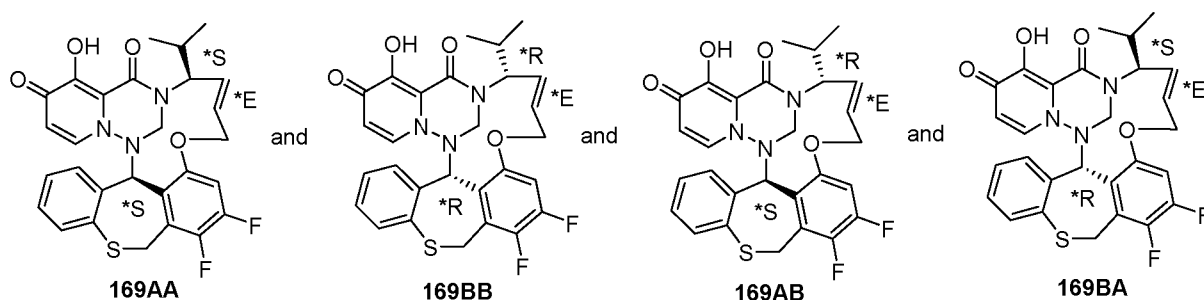
LC/MS (method LC-C): Rt 2.80 min, MH⁺ 537

[α]_D²⁰: -471.01 ° (c 0.069, DMF)

Chiral HPLC (method HPLC-B): Rt 7.34 min, chiral purity 100%

Example 169: synthesis of (9*S,17a*S,*E)-24,25-difluoro-12-hydroxy-9-isopropyl-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **169AA**) and (9*R,17a*R,*E)-24,25-difluoro-12-hydroxy-9-isopropyl-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **169BB**) and (9*R,17a*S,*E)-24,25-difluoro-12-hydroxy-9-isopropyl-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **169AB**) and (9*S,17a*R,*E)-24,25-difluoro-12-hydroxy-9-

isopropyl-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **169BA**)



Compounds **169AA**, **169BB**, **169AB** and **169BA** were synthesized according to the procedures described in example **159** starting from intermediate 5-(benzyloxy)-3-(4-methylpent-1-en-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (see example **124**).

Compound 169AA:

LC/MS (method LC-C): Rt 3.30 min, MH⁺ 538

[α]_D²⁰: +120.41 ° (c 0.196, DMF)

Chiral HPLC (method HPLC-B): Rt 4.46 min, chiral purity 100%

Compound 169BB:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.33 - 12.74 (m, 1 H) 7.38 (br dd, *J*=11.8, 6.9 Hz, 1 H) 7.07 - 7.24 (m, 3 H) 6.84 (br t, *J*=6.9 Hz, 1 H) 6.46 - 6.63 (m, 2 H) 6.17 - 6.34 (m, 1 H) 5.95 (s, 1 H) 5.56 - 5.71 (m, 2 H) 5.13 (d, *J*=13.4 Hz, 1 H) 4.80 (br dd, *J*=9.9, 6.8 Hz, 1 H) 4.53 (br d, *J*=13.6 Hz, 1 H) 4.40 (br t, *J*=9.0 Hz, 1 H) 4.05 (d, *J*=14.3 Hz, 1 H) 3.60 (br t, *J*=9.6 Hz, 1 H) 2.31 - 2.43 (m, 1 H) 0.76 - 0.95 (m, 6 H)

LC/MS (method LC-C): Rt 3.30min, MH⁺ 538

[α]_D²⁰: -120.35 ° (c, DMF)

Chiral HPLC (method HPLC-B): Rt 8.09 min, chiral purity 100%

Compound 169AB:

LC/MS (method LC-C): Rt 3.18 min, MH⁺ 538

[α]_D²⁰: +420.13 ° (c 0.159, DMF)

Chiral HPLC (method HPLC-B): Rt 4.84 min, chiral purity 100%

Compound 169BA:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.65 - 12.25 (m, 1 H) 7.41 (br dd, *J*=11.7, 7.3 Hz, 1 H) 7.26 (d, *J*=7.6 Hz, 1 H) 7.11 - 7.17 (m, 1 H) 7.03 - 7.10 (m, 1 H) 6.84 - 6.93 (m, 1 H) 6.81 (d, *J*=6.9 Hz, 1 H) 6.35 (ddd, *J*=15.5, 9.7, 5.7 Hz, 1 H) 5.75 (dd, *J*=15.8, 6.9 Hz, 1 H) 5.66 (dd, *J*=14.0, 1.7 Hz, 1 H) 5.61 (d, *J*=7.9 Hz, 1 H) 5.26 (s, 1 H) 5.05 (d, *J*=13.6 Hz, 1 H) 4.85 (dt, *J*=10.9, 5.3 Hz, 2 H) 4.47 (d, *J*=13.9 Hz, 1 H) 4.31 (t, *J*=10.7 Hz, 1 H) 4.12 (d, *J*=14.2 Hz, 1 H) 1.80 (tt, *J*=12.3, 6.5 Hz, 1 H) 0.85 (dd, *J*=10.6, 6.5 Hz, 6 H)

LC/MS (method LC-C): Rt 3.19 min, MH⁺ 538

[α]_D²⁰: -387.50 ° (c 0.144, DMF)

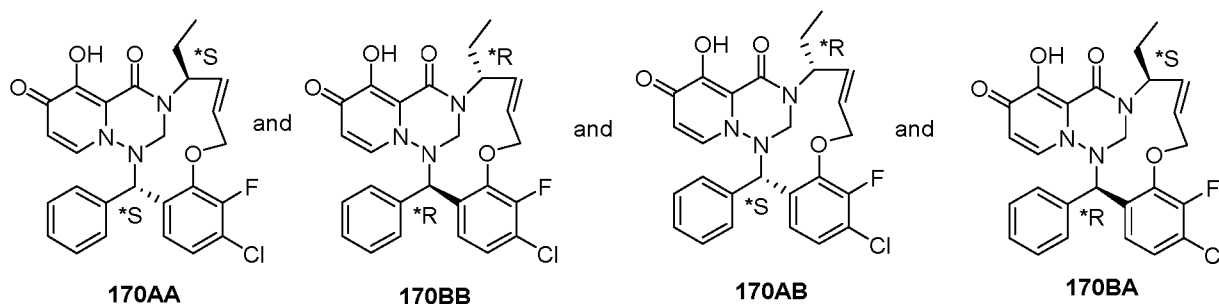
Chiral HPLC (method HPLC-B): Rt 7.93 min, chiral purity 100%

Example 170: synthesis of (9*S,18*S,E)-3-chloro-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **170AA**) and (9*R,18*R,E)-3-chloro-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione

(Compound **170BB**) and (9*R,18*S,E)-3-chloro-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-

f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **170AB**) and (9*S,18*R,E)-3-chloro-9-ethyl-4-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **170BA**)



Compounds **170AA**, **170BB**, **170AB** and **170BA** were synthesized according to the procedures described in example 39 starting from intermediate 2-(allyloxy)-4-chloro-1-(chloro(phenyl)methyl)-3-fluorobenzene (synthesized as **74c** from 4-chloro-3-fluoro-2-hydroxy-benzaldehyde [CAS 1427431-22-8]).

Compound 170AA:LC/MS (method LC-C): Rt 3.14 min, MH⁺ 496[α]_D²⁰: +607.87 ° (c 0.178, DMF)

Chiral HPLC (method HPLC-B): Rt 4.64 min, chiral purity 100%

5

Compound 170BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.61 - 11.48 (m, 1 H) 7.96 (d, *J*=8.2 Hz, 1 H) 7.61 (dd, *J*=8.5, 7.3 Hz, 1 H) 7.02 - 7.28 (m, 6 H) 6.37 (ddd, *J*=15.7, 10.3, 5.2 Hz, 1 H) 5.68 (br dd, *J*=15.3, 6.1 Hz, 1 H) 5.47 (d, *J*=7.6 Hz, 1 H) 5.13 - 5.23 (m, 2 H) 5.05 (d, *J*=13.6 Hz, 1 H) 4.91 (dd, *J*=11.3, 5.0 Hz, 1 H) 4.25 (d, *J*=13.6 Hz, 1 H) 4.06 (br t, *J*=10.6 Hz, 1 H) 1.40 - 1.63 (m, 2 H) 0.83 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.14 min, MH⁺ 496[α]_D²⁰: -621.31 ° (c 0.183, DMF)

Chiral HPLC (method HPLC-B): Rt 7.09 min, chiral purity 100%

15

Compound 170AB:LC/MS (method LC-C): Rt 3.19 min, MH⁺ 496[α]_D²⁰: +709.9 ° (c 0.192, DMF)

Chiral HPLC (method HPLC-A): Rt 4.57 min, chiral purity 100%

20

Compound 170BA:

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.01 (d, *J*=8.2 Hz, 1 H) 7.61 (dd, *J*=8.6, 7.2 Hz, 1 H) 7.35 (d, *J*=7.6 Hz, 1 H) 7.00 - 7.25 (m, 5 H) 6.39 - 6.55 (m, 1 H) 5.84 - 6.08 (m, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.39 (s, 1 H) 5.20 (d, *J*=13.9 Hz, 1 H) 4.64 - 4.75 (m, 1 H) 4.58 (br dd, *J*=10.0, 4.5 Hz, 1 H) 4.24 (d, *J*=14.1 Hz, 1 H) 3.40 - 3.50 (m, 1 H) 2.33 (br t, *J*=6.8 Hz, 1 H) 2.07 - 2.22 (m, 1 H) 0.86 (t, *J*=7.3 Hz, 3 H)

LC/MS (method LC-C): Rt 3.19 min, MH⁺ 496[α]_D²⁰: -707.14 ° (c 0.252, DMF)

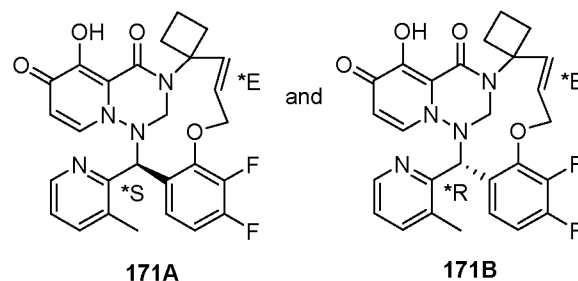
Chiral HPLC (method HPLC-A): Rt 6.67 min, chiral purity 100%

30

Example 171: synthesis of (18'^{*}S,*E)-3',4'-difluoro-12'-hydroxy-18'-(3-methylpyridin-2-yl)-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **171A**) and (18'^{*}R,*E)-3',4'-difluoro-12'-hydroxy-18'-(3-methylpyridin-2-yl)-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **171B**)

35

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Compounds **171A** and **171B** were synthesized according to the procedures described in example **146** starting from intermediate 2-((2-(allyloxy)-3,4-difluorophenyl)chloromethyl)-3-methylpyridine (synthesized as **45b** from 2-bromo-3-methyl-pyridine [CAS 3430-17-9] and **74a**).

Compound **171A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.34 (br d, *J*=4.1 Hz, 1 H) 7.98 (br t, *J*=7.1 Hz, 1 H) 7.42 (br d, *J*=7.6 Hz, 1 H) 7.32 - 7.40 (m, 1 H) 7.22 (br d, *J*=7.6 Hz, 1 H) 7.07 (dd, *J*=7.6, 4.7 Hz, 1 H) 6.55 (br d, *J*=15.4 Hz, 1 H) 6.17 - 6.28 (m, 1 H) 5.79 (s, 1 H) 5.54 (d, *J*=7.9 Hz, 1 H) 5.13 (d, *J*=13.6 Hz, 1 H) 4.88 (br t, *J*=9.8 Hz, 1 H) 4.59 - 4.69 (m, 1 H) 3.89 (br d, *J*=13.9 Hz, 1 H) 2.81 - 2.89 (m, 1 H) 2.26 (s, 3 H) 2.03 - 2.19 (m, 3 H) 1.70 - 1.81 (m, 1 H) 1.55 - 1.67 (m, 1 H)

LC/MS (method LC-C): Rt 2.98 min, MH⁺ 507

[α]_D²⁰: -650.65 ° (c 0.077, DMF)

Chiral HPLC (method HPLC-B): Rt 5.34 min, chiral purity 100%

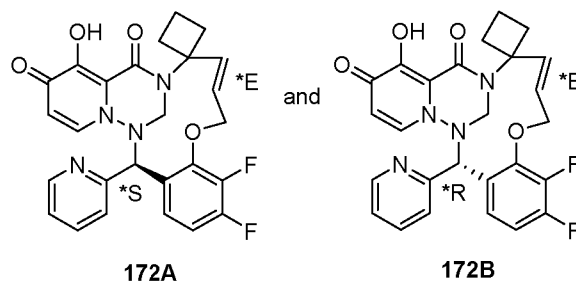
Compound **171B**:

LC/MS (method LC-C): Rt 2.98 min, MH⁺ 507

[α]_D²⁰: +650.62 ° (c 0.081, DMF)

Chiral HPLC (method HPLC-B): Rt 7.22 min, chiral purity 100%

Example 172: synthesis of (18'*S*,**E*)-3',4'-difluoro-12'-hydroxy-18'-(pyridin-2-yl)-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **172A**) and (18'*R*,**E*)-3',4'-difluoro-12'-hydroxy-18'-(pyridin-2-yl)-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **172B**)



Compounds **172A** and **172B** were synthesized according to the procedures described in example **146** starting from intermediate 2-((2-(allyloxy)-3,4-difluorophenyl)chloromethyl)pyridine (synthesized as **45b** from 2-bromo-pyridine [CAS 109-04-6] and **74a**).

Compound **172A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.36 (br d, *J*=4.1 Hz, 1 H) 7.95 (br t, *J*=7.1 Hz, 1 H) 7.62 (td, *J*=7.6, 1.4 Hz, 1 H) 7.38 - 7.49 (m, 1 H) 7.13 - 7.25 (m, 3 H) 6.51 (br d, *J*=15.8 Hz, 1 H) 6.19 (dt, *J*=15.1, 7.3 Hz, 1 H) 5.50 (d, *J*=7.6 Hz, 1 H) 5.42 (s, 1 H) 5.11 (d, *J*=13.6 Hz, 1 H) 4.82 (br t, *J*=9.6 Hz, 1 H) 4.52 - 4.65 (m, 1 H) 3.86 (d, *J*=13.6 Hz, 1 H) 2.83 - 2.92 (m, 1 H) 2.42 - 2.47 (m, 1 H) 2.02 - 2.17 (m, 2 H) 1.75 (br d, *J*=8.5 Hz, 1 H) 1.52 - 1.67 (m, 1 H)

LC/MS (method LC-C): Rt 2.74 min, MH⁺ 493

[α]_D²⁰: -589.04 ° (c 0.073, DMF)

Chiral HPLC (method HPLC-B): Rt 5.09 min, chiral purity 100%

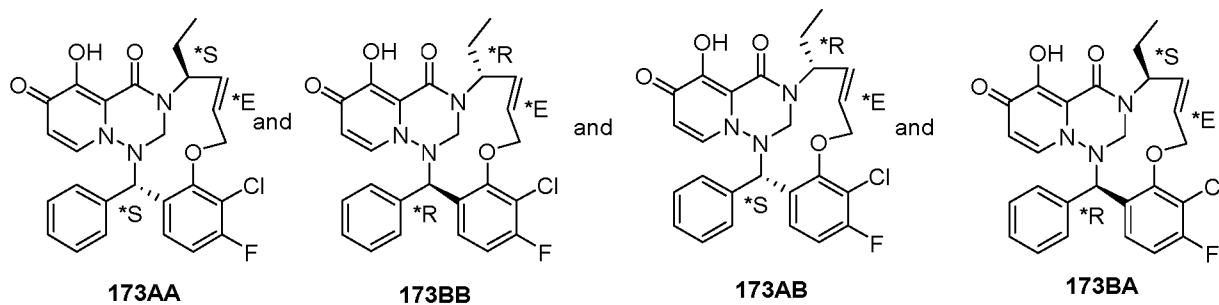
Compound **172B**:

LC/MS (method LC-C): Rt 2.73 min, MH⁺ 493

[α]_D²⁰: +620.00 ° (c 0.080, DMF)

Chiral HPLC (method HPLC-B): Rt 5.57 min, chiral purity 100%

Example 173: synthesis of (9*S,18*S,*E)-4-chloro-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **173AA**) and (9*R,18*R,*E)-4-chloro-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **173BB**) and (9*R,18*S,*E)-4-chloro-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **173AB**) and (9*S,18*R,*E)-4-chloro-9-ethyl-3-fluoro-12-hydroxy-18-phenyl-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **173BA**)



Compounds **173AA**, **173BB**, **173AB** and **173BA** were synthesized according to the procedures described in example **39** starting from intermediate 2-(allyloxy)-3-chloro-1-(chloro(phenyl)methyl)-4-fluorobenzene (synthesized as **74c** from 3-chloro-4-fluoro-2-hydroxy-benzaldehyde [CAS 1260826-10-5]).

Compound 173AA:

LC/MS (method LC-C): Rt 3.13 min, MH⁺ 496
 $[\alpha]_D^{20}$: +585.00 ° (c 0.120, DMF)

Compound 173BB:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.90 - 11.04 (m, 1 H) 8.18 (dd, *J*=8.5, 6.6 Hz, 1 H) 7.49 (t, *J*=8.7 Hz, 1 H) 7.32 (d, *J*=7.6 Hz, 1 H) 6.93 - 7.26 (m, 5 H) 6.36 - 6.58 (m, 1 H) 5.79 - 6.00 (m, 1 H) 5.49 (d, *J*=7.6 Hz, 1 H) 5.41 (s, 1 H) 5.22 (d, *J*=13.9 Hz, 1 H) 4.79 - 4.94 (m, 1 H) 4.64 - 4.76 (m, 1 H) 4.27 (d, *J*=13.9 Hz, 1 H) 3.40 - 3.49 (m, 1 H) 2.28 - 2.38 (m, 1 H) 2.06 - 2.24 (m, 1 H) 0.87 (t, *J*=7.4 Hz, 3 H)
 LC/MS (method LC-C): Rt 3.13 min, MH⁺ 496
 $[\alpha]_D^{20}$: -620.73 ° (c 0.164, DMF)

Compound 173AB:

LC/MS (method LC-C): Rt 3.09 min, MH⁺ 496
 $[\alpha]_D^{20}$: +595.45 ° (c 0.088, DMF)
 Chiral HPLC (method HPLC-B): Rt 4.68 min, chiral purity 100%

Compound 173BA:

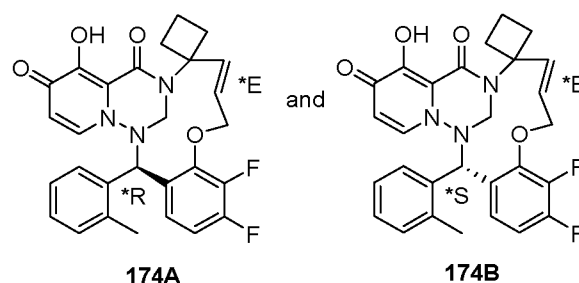
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.09 - 8.22 (m, 1 H) 7.50 (br t, *J*=8.7 Hz, 1 H) 6.94 - 7.38 (m, 6 H) 6.30 - 6.52 (m, 1 H) 5.64 (br dd, *J*=14.7, 5.2 Hz, 1 H) 5.48 (br d, *J*=7.9 Hz, 1 H) 5.12 - 5.29 (m, 2 H) 5.06 (br d, *J*=13.6 Hz, 1 H) 4.91 (br dd, *J*=11.3, 4.7 Hz, 1 H) 4.27 (br d, *J*=13.6 Hz, 1 H) 4.13 (br t, *J*=10.9 Hz, 1 H) 1.40 - 1.62 (m, 2 H) 0.84 (br t, *J*=7.1 Hz, 3 H)

LC/MS (method LC-C): Rt 3.09 min, MH⁺ 496

$[\alpha]_D^{20}$: -579.38 ° (c 0.097, DMF)

Chiral HPLC (method HPLC-B): Rt 5.50 min, chiral purity 100%

- 5 **Example 174:** synthesis of (18'^{*}R,^{*}E)-3',4'-difluoro-12'-hydroxy-18'-(o-tolyl)-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **174A**) and (18'^{*}S,^{*}E)-3',4'-difluoro-12'-hydroxy-18'-(o-tolyl)-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **174B**)



- Compounds **174A** and **174B** were synthesized according to the procedures described in example **146** starting from intermediate 2-(allyloxy)-1-(chloro(o-tolyl)methyl)-3,4-difluorobenzene (see example 155).

Compound **174A**:

LC/MS (method LC-G): Rt 3.19min, MH⁺ 506

$[\alpha]_D^{20}$: +637.58° (c 0.165, DMF)

- 20 Chiral HPLC (method HPLC-B): Rt 5.53 min, chiral purity 100%

Compound **174B**:

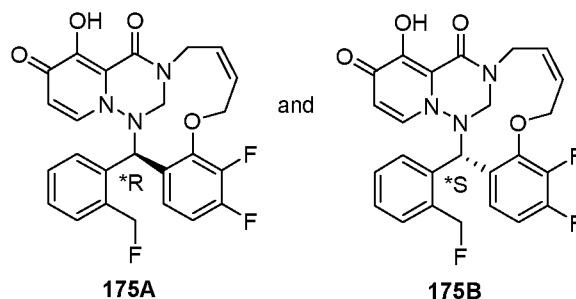
- ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.67 - 11.20 (m, 1 H) 7.97 (br t, *J*=6.9 Hz, 1 H) 7.49 (d, *J*=7.6 Hz, 1 H) 7.37 - 7.46 (m, 2 H) 6.99 - 7.10 (m, 2 H) 6.94 - 6.99 (m, 1 H) 6.49 (br d, *J*=16.1 Hz, 1 H) 6.11 - 6.24 (m, 1 H) 5.65 (s, 1 H) 5.52 (d, *J*=7.6 Hz, 1 H) 5.14 (d, *J*=13.6 Hz, 1 H) 4.87 (br t, *J*=9.6 Hz, 1 H) 4.59 (br s, 1 H) 3.87 (d, *J*=13.6 Hz, 1 H) 2.79 - 2.92 (m, 1 H) 2.42 - 2.47 (m, 1 H) 2.26 (s, 3 H) 2.00 - 2.17 (m, 2 H) 1.76 (q, *J*=9.0 Hz, 1 H) 1.53 - 1.68 (m, 1 H)

LC/MS (method LC-G): Rt 3.19 min, MH⁺ 506

- 30 $[\alpha]_D^{20}$: -637.43 ° (c 0.179, DMF)

Chiral HPLC (method HPLC-B): Rt 4.84 min, chiral purity 100%

Example 175: synthesis of (18*R,Z)-3,4-difluoro-18-(2-(fluoromethyl)phenyl)-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **175A**) and (18*S,Z)-3,4-difluoro-18-(2-(fluoromethyl)phenyl)-12-hydroxy-6,9-dihydro-18H-10,17-methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **175B**)



Compounds **175A** and **175B** were synthesized according to the procedures described in example 5 starting from intermediate 2-(allyloxy)-1-(chloro(2-(fluoromethyl)phenyl)methyl)-3,4-difluorobenzene (synthesized as **74c** from 1-bromo-2-(fluoromethyl)benzene [CAS 446-47-9]).

Compound **175A**:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.96 - 8.05 (m, 1 H) 7.80 (br d, *J*=7.9 Hz, 1 H) 7.48 (q, *J*=8.8 Hz, 1 H) 7.30 - 7.43 (m, 2 H) 7.19 - 7.28 (m, 2 H) 6.12 - 6.28 (m, 1 H) 5.90 - 6.10 (m, 1 H) 5.48 - 5.70 (m, 3 H) 5.22 - 5.40 (m, 1 H) 5.17 (br d, *J*=13.9 Hz, 1 H) 4.95 (br s, 1 H) 4.82 (br dd, *J*=14.0, 4.6 Hz, 1 H) 4.33 (br d, *J*=13.9 Hz, 2 H) 3.17 - 3.22 (m, 1 H)

LC/MS (method LC-G): Rt 2.67 min, MH⁺ 484

[α]_D²⁰: -639.76 ° (c 0.083, DMF)

Chiral HPLC (method HPLC-A): Rt 4.88 min, chiral purity 100%

Compound **175B**:

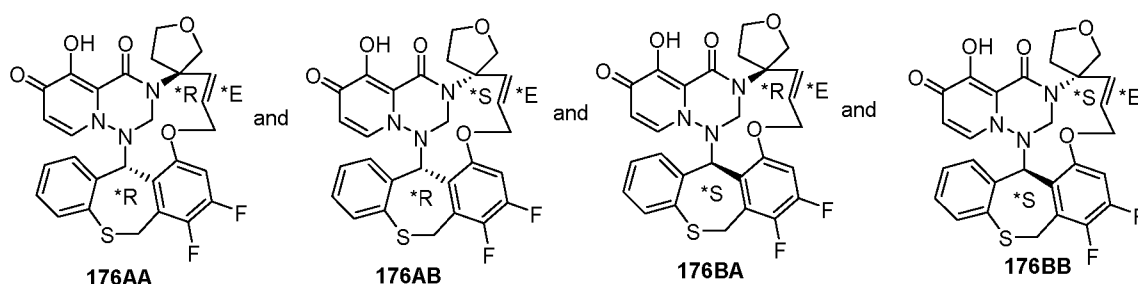
LC/MS (method LC-G): Rt 2.67 min, MH⁺ 484

[α]_D²⁰: +658.67° (c 0.075, DMF)

Chiral HPLC (method HPLC-A): Rt 5.60 min, chiral purity 100%

Example 176: synthesis of (3*R,17a*R,*E)-24',25'-difluoro-12'-hydroxy-2',4,5,17a'-tetrahydro-2H,6'H-spiro[furan-3,9'-[3,4](epi)prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **176AA**) and (3*S,

17a'*R,*E)-24',25'-difluoro-12'-hydroxy-2',4,5,17a'-tetrahydro-2H,6'H-spiro[furan-3,9'-
 [3,4](epi)prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-
 f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **176AB**) and (3*R,
 17a'*S,*E)-24',25'-difluoro-12'-hydroxy-2',4,5,17a'-tetrahydro-2H,6'H-spiro[furan-3,9'-
 [3,4](epi)prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-
 f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **176BA**) and (3*S,
 17a'*S,*E)-24',25'-difluoro-12'-hydroxy-2',4,5,17a'-tetrahydro-2H,6'H-spiro[furan-3,9'-
 [3,4](epi)prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-
 f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **176BB**)



Compounds **176AA**, **176AB**, **176BA** and **176BB** were synthesized according to the
 procedures described in example **159** starting from intermediate 5-(benzyloxy)-3-(3-
 vinyltetrahydrofuran-3-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione
 (synthesized as **146f** from N-(3-formyltetrahydro-3-furanyl)carbamic acid-1,1-dimethyl
 ester [CAS 2170650-09-4]).

Compound **176AA**:

LC/MS (method LC-D): Rt 2.31 min, MH⁺ 552
 $[\alpha]_D^{20}$: +357.98 ° (c 0.238, DMF)

Compound **176AB**:

LC/MS (method LC-D): Rt 1.34 min, MH⁺ 552
 $[\alpha]_D^{20}$: +359.71 ° (c, DMF)

Compound **176BA**:

¹H NMR (400 MHz, DMSO-d₆) δ 7.48 (dd, J = 11.9, 7.3 Hz, 1H), 7.38 (d, J = 7.6 Hz,
 1H), 7.16 – 7.01 (m, 2H), 6.88 (td, J = 7.4, 1.4 Hz, 1H), 6.76 (dd, J = 7.8, 1.5 Hz, 1H),
 6.40 (dt, J = 15.3, 7.4 Hz, 1H), 6.17 (d, J = 15.9 Hz, 1H), 5.76 – 5.58 (m, 2H), 5.38 (s,
 1H), 5.12 (d, J = 13.7 Hz, 1H), 4.81 (dd, J = 11.2, 7.1 Hz, 1H), 4.54 (dd, J = 11.2, 7.9 Hz,
 1H), 4.27 (d, J = 13.7 Hz, 1H), 4.11 (d, J = 14.1 Hz, 1H), 4.02 (d, J = 8.5 Hz, 1H), 3.88

(td, J = 8.0, 4.6 Hz, 1H), 3.68 (q, J = 8.2 Hz, 1H), 3.55 (d, J = 8.5 Hz, 1H), 2.98 – 2.75 (m, 2H).

LC/MS (method LC-D): Rt 2.31 min, MH⁺ 552

[α]_D²⁰: -346.45 ° (c 0.211, DMF)

5

Compound 176BB:

¹H NMR (400 MHz, DMSO-d₆) d 7.53 (dd, J = 11.8, 7.3 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.13 (ddd, J = 8.5, 7.1, 1.4 Hz, 1H), 7.06 (dd, J = 8.0, 1.4 Hz, 1H), 6.88 (td, J = 7.4, 1.4 Hz, 1H), 6.75 (dd, J = 7.8, 1.5 Hz, 1H), 6.41 – 6.23 (m, 2H), 5.77 – 5.67 (m, 2H), 5.39 (s, 1H), 5.21 (d, J = 13.8 Hz, 1H), 4.79 (dd, J = 11.2, 7.1 Hz, 1H), 4.68 – 4.54 (m, 2H), 4.38 (d, J = 13.8 Hz, 1H), 4.19 – 4.00 (m, 2H), 3.78 (td, J = 9.0, 2.5 Hz, 1H), 3.61 (td, J = 8.8, 6.7 Hz, 1H), 2.38 (td, J = 8.1, 6.9, 3.5 Hz, 1H), 2.16 – 1.92 (m, 1H).

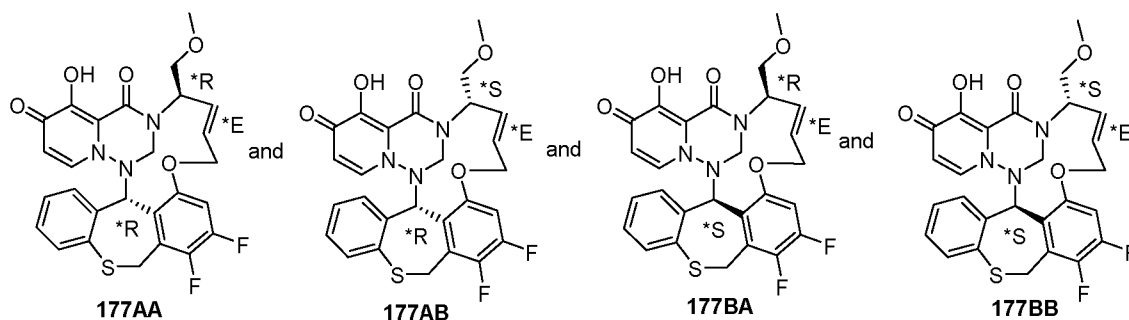
LC/MS (method LC-D): Rt 1.32 min, MH⁺ 552

[α]_D²⁰: -392.79 ° (c 0.208, DMF)

15

Example 177: synthesis of (9*R,17a*R,*E)-24,25-difluoro-12-hydroxy-9-(methoxymethyl)-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **177AA**) and (9*S,17a*R,*E)-24,25-difluoro-12-hydroxy-9-(methoxymethyl)-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **177AB**) and (9*R,17a*S,*E)-24,25-difluoro-12-hydroxy-9-(methoxymethyl)-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **177BA**) and (9*S,17a*S,*E)-24,25-difluoro-12-hydroxy-9-(methoxymethyl)-2,6,9,17a-tetrahydro-3,4-(epiprop[1]en[1]yl[3]ylidene)-10,17-methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine-11,13-dione (Compound **177BB**)

30



Compounds **177AA**, **177AB**, **177BA** and **177BB** were synthesized according to the procedures described in example **159** starting from intermediate 5-(benzyloxy)-3-(1-methoxybut-3-en-2-yl)-2,3-dihydro-1H-pyrido[2,1-f][1,2,4]triazine-4,6-dione (see example **150**).

5

Compound 177AA:LC/MS (method LC-D): Rt 1.37 min, MH⁺ 540[α]_D²⁰: +308.06 ° (c 0.211, DMF)10 **Compound 177AB:**

¹H NMR (400 MHz, DMSO-d₆) δ 7.44 (dd, J = 11.7, 7.2 Hz, 1H), 7.36 – 7.23 (m, 1H), 7.22 – 7.06 (m, 2H), 6.88 (q, J = 5.7, 4.8 Hz, 2H), 6.40 (ddd, J = 15.8, 10.4, 5.6 Hz, 1H), 5.81 – 5.59 (m, 3H), 5.50 (q, J = 6.7 Hz, 1H), 5.30 (s, 1H), 5.01 (d, J = 14.0 Hz, 1H), 4.89 (dd, J = 11.3, 5.3 Hz, 1H), 4.49 (d, J = 13.9 Hz, 1H), 4.31 (t, J = 10.8 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 3.58 – 3.41 (m, 2H), 3.24 (s, 3H).

15

LC/MS (method LC-D): Rt 1.37 min, MH⁺ 540[α]_D²⁰: -278.67 ° (c 0.211, DMF)**Compound 177BA:**

¹H NMR (400 MHz, DMSO-d₆) δ 7.57 (dd, J = 12.0, 7.0 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.14 (dtd, J = 16.2, 8.1, 1.5 Hz, 2H), 6.84 (td, J = 7.4, 1.6 Hz, 1H), 6.66 (dd, J = 7.9, 1.4 Hz, 1H), 6.26 – 6.14 (m, 1H), 5.94 – 5.78 (m, 2H), 5.65 (d, J = 7.6 Hz, 1H), 5.55 (dd, J = 14.2, 2.7 Hz, 1H), 5.45 – 5.35 (m, 1H), 4.98 – 4.82 (m, 3H), 4.27 (d, J = 13.5 Hz, 1H), 4.01 (d, J = 14.2 Hz, 1H), 3.64 (dd, J = 9.6, 5.5 Hz, 1H), 3.49 (dd, J = 9.6, 3.4 Hz, 1H), 3.27 (s, 3H).

25

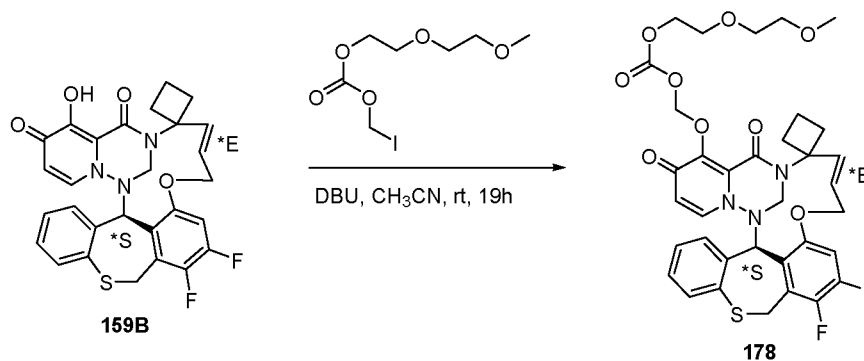
LC/MS (method LC-D): Rt 1.42 min, MH⁺ 540**Compound 177BB:**LC/MS (method LC-D): Rt 1.40 min, MH⁺ 540

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Example 178: synthesis of (((17a'*S,*E)-24',25'-difluoro-11',13'-dioxo-2',11',13',17a'-tetrahydro-6'H-spiro[cyclobutane-1,9'-[3,4](epi)prop[1]en[1]yl[3]ylidene][10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin]-12'-yl)oxy)methyl (2-(2-methoxyethoxy)ethyl) carbonate (Compound **178**)

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**Synthesis of compound 178:**

To a solution of compound **159B** (250 mg, 0.467 mmol) in dry CH₃CN (3 mL) was added a solution of iodomethyl (2-(2-methoxyethoxy)ethyl) carbonate [CAS 854924-77-9] (426 mg, 1.40 mmol) in dry CH₃CN (2 mL) and DBU (209 μ L, 1.4 mmol). The reaction was stirred at rt for 19h and was then diluted with AcOEt and washed with H₂O, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (40 g, Eluent: CH₂Cl₂/MeOH 0 to 10%; 2 times) then over C18 (30 g, Eluent: H₂O/MeOH 0 to 100%) to compound **178** (184 mg) as a white solid.

Compound 178:

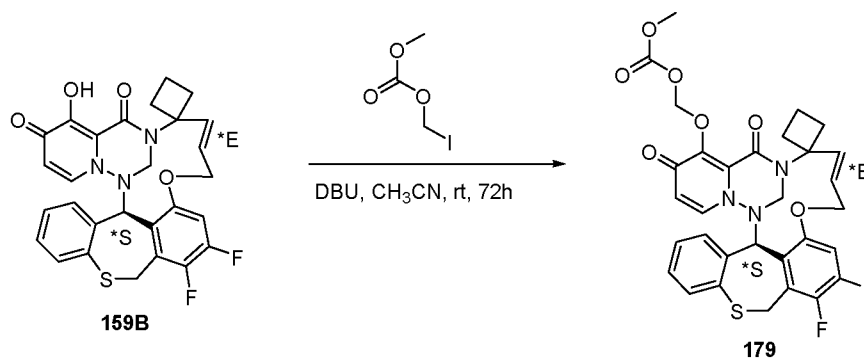
¹H NMR (400 MHz, DMSO-d₆) δ 7.57 – 7.51 (m, 2H), 7.13 – 7.03 (m, 2H), 6.88 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 15.8 Hz, 1H), 6.25 – 6.17 (m, 1H), 5.85 (d, J = 7.8 Hz, 1H), 5.75 – 5.72 (m, 1H), 5.69 (d, J = 6.5 Hz, 1H), 5.57 (d, J = 6.5 Hz, 1H), 5.36 (s, 1H), 5.08 (d, J = 14.0 Hz, 1H), 4.70 (d, J = 7.2 Hz, 2H), 4.30 – 4.20 (m, 2H), 4.09 (d, J = 14.2 Hz, 1H), 3.99 (d, J = 14.0 Hz, 1H), 3.69 (t, J = 4.6 Hz, 2H), 3.56 – 3.54 (m, 2H), 3.44 – 3.41 (m, 2H), 3.22 (s, 3H), 2.61 – 2.55 (m, 1H), 2.46 – 2.44 (m, 1H), 2.12 (brs, 1H), 2.01 (dd, J = 20.7, 10.2 Hz, 1H), 1.78 – 1.73 (m, 1H), 1.65 – 1.56 (m, 1H).

LC/MS (method LC-F): Rt 4.91 min, MH⁺ 712

Chiral SFC (method SFC-B): Rt 1.25 min, chiral purity 99.87%.

Example 179: synthesis of (((17a'S,E)-24',25'-difluoro-11',13'-dioxo-2',11',13',17a'-tetrahydro-6'H-spiro[cyclobutane-1,9'-[3,4](epi)prop[1]en[1]yl[3]ylidene][10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin]-12'-yl)oxy)methyl methyl carbonate (Compound **179**)

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**Synthesis of compound 179:**

A mixture of compound **159B** (447 mg, 0.835 mmol), iodomethyl methyl carbonate [CAS 69862-08-4] (451 mg, 2.087 mmol) and DBU (311 μ L, 2.087 mmol) in CH₃CN (7 mL) was stirred at rt for 72 h. The mixture was diluted with water and was extracted with EtOAc. The organic layer was washed with water then with brine. The organic layer was dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. Purification was carried out by flash chromatography over silica gel (24 g 30 μ m (CH₂Cl₂/CH₃OH 99/1 to 97/3)). The pure fractions were collected and evaporated to dryness to give, after crystallisation from CH₃OH, 270 mg of compound **179**.

Compound 179:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.50 - 7.59 (m, 2 H) 7.09 - 7.15 (m, 1 H) 7.02 - 7.07 (m, 1 H) 6.88 (td, *J*=7.4, 0.9 Hz, 1 H) 6.72 - 6.77 (m, 1 H) 6.49 (d, *J*=15.8 Hz, 1 H) 6.21 (dt, *J*=15.3, 7.5 Hz, 1 H) 5.85 (d, *J*=7.9 Hz, 1 H) 5.74 (dd, *J*=14.5, 1.9 Hz, 1 H) 5.67 (d, *J*=6.6 Hz, 1 H) 5.54 (d, *J*=6.6 Hz, 1 H) 5.36 (s, 1 H) 5.08 (d, *J*=13.9 Hz, 1 H) 4.66 - 4.77 (m, 2 H) 4.09 (d, *J*=14.2 Hz, 1 H) 4.00 (d, *J*=13.9 Hz, 1 H) 3.77 (s, 3 H) 2.54 - 2.62 (m, 1 H) 2.41 - 2.47 (m, 1 H) 2.09 - 2.18 (m, 1 H) 2.01 (q, *J*=10.2 Hz, 1 H) 1.70 - 1.80 (m, 1 H) 1.54 - 1.67 (m, 1 H)

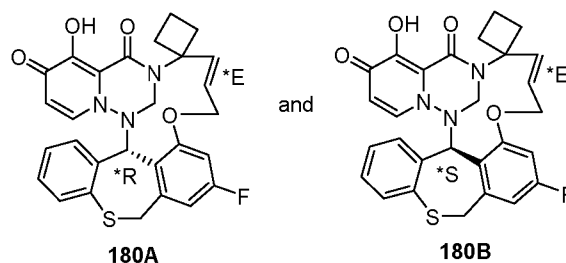
LC/MS (method LC-A): Rt 2.99 min, MH⁺ 624

Chiral SFC (method SFC-B): Rt 1.37 min, chiral purity 99.71%.

Example 180: synthesis of (17a'*R,*E)-24'-fluoro-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9']-

[3,4](epi-prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **180A**) and (17a'*S,*E)-24'-fluoro-12'-hydroxy-2',17a'-dihydro-6'H-spiro[cyclobutane-1,9']-[3,4](epi-prop[1]en[1]yl[3]ylidene)[10,17]methanobenzo[6,7]thiepino[4,5-c]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecine]-11',13'-dione (Compound **180B**)

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Compounds **180A** and **180B** were synthesized according to the procedures described in example **159** starting from intermediate 10-(allyloxy)-11-chloro-8-fluoro-6,11-dihydrodibenzo[b,e]thiepine (synthesized as **88n** from 4-fluoro-2-methyl-benzoic acid [CAS 321-21-1]).

Compound **180A**:

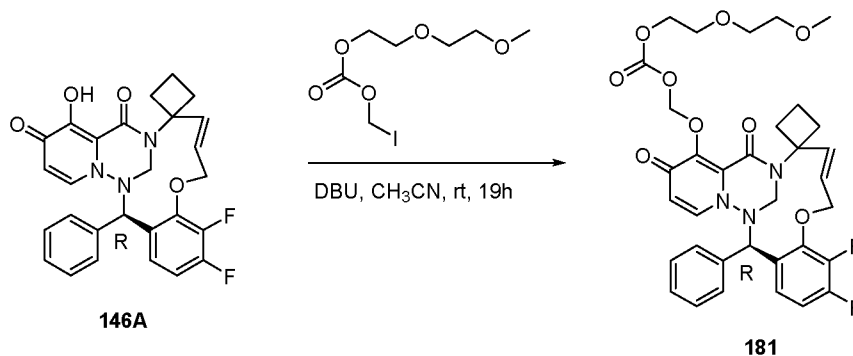
LC/MS (method LC-D): Rt 1.45 min, MH⁺ 518

Compound **180B**:

¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 7.47 (d, J=7.6 Hz, 1H), 7.26 - 7.29 (m, 1H), 7.07 - 7.13 (m, 2H), 7.02 (d, J=6.8 Hz, 1H), 6.83 (t, J=7.6 Hz, 1H), 6.68 (d, J=6.8 Hz, 1H), 6.47 (d, J=7.2 Hz, 1H), 6.14 - 6.22 (m, 1H), 5.87 (d, J=6.8 Hz, 1H), 5.73 (d, J=7.6 Hz, 1H), 5.37 (s, 1H), 5.12 (d, J=7.2 Hz, 1H), 4.75 (d, J=5.6 Hz, 2H), 3.85 - 3.94 (m, 2H), 2.76 - 2.82 (m, 1H), 2.45 (d, J=7.6 Hz, 1H), 2.10 (t, J=6.8 Hz, 2H), 1.72 - 1.76 (m, 1H), 1.59-1.64 (m, 1H)

LC/MS (method LC-D): Rt 1.45 min, MH⁺ 518

Example 181: synthesis of (((18'R,E)-3',4'-difluoro-11',13'-dioxo-18'-phenyl-11',13'-dihydro-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin]-12'-yl)oxy)methyl (2-(2-methoxyethoxy)ethyl) carbonate (Compound **181**)



Synthesis of compound **181**:

To a solution of compound **146A** (161 mg, 0.328 mmol) in dry CH₃CN (2.1 mL) were added a solution of iodomethyl (2-(2-methoxyethoxy)ethyl) carbonate [CAS 854924-77-

9] (374 mg, 0.983 mmol) in dry CH₃CN (1.7 mL) and DBU (0.147 mL, 0.983 mmol). The reaction mixture was stirred for 19h at rt, was diluted with AcOEt and then washed with H₂O, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica (40g, Eluent: CH₂Cl₂/MeOH 0 to 10%). The compound was purified again over silica (C18 12 g (eluent H₂O/MeOH 50:50 to 0:100) to afford compound **181** (107 mg).

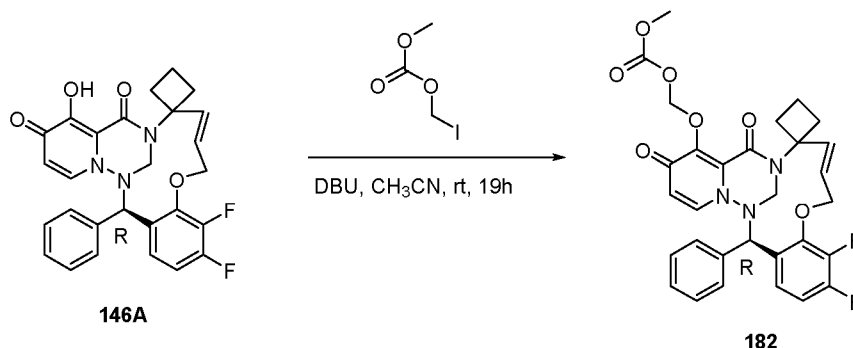
Compound 181:

¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.58 (m, 1H), 7.20 – 7.09 (m, 4H), 7.01 (d, *J* = 3.7 Hz, 2H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.42 (brs, 1H), 6.07 (brs, 1H), 5.95 (d, *J* = 6.3 Hz, 1H), 5.80 (d, *J* = 6.3 Hz, 1H), 5.76 (d, *J* = 7.8 Hz, 1H), 5.30 (s, 1H), 4.84 (d, *J* = 13.6 Hz, 1H), 4.75 – 4.65 (m, 1H), 4.59 (brs, 1H), 4.48 – 4.30 (m, 2H), 3.88 (d, *J* = 13.6 Hz, 1H), 3.79 (t, *J* = 5.0 Hz, 2H), 3.66 (dd, *J* = 5.6, 3.6 Hz, 2H), 3.51 (dd, *J* = 5.6, 3.7 Hz, 2H), 3.34 (s, 3H), 2.87 – 2.80 (m, 1H), 2.67 – 2.51 (m, 1H), 2.01 – 1.95 (m, 2H), 1.89 – 1.77 (m, 1H), 1.76 – 1.63 (m, 1H).

LC/MS (method LC-E): Rt 3.36 min, MH⁺ 668

Chiral SFC (method SFC-C): Rt 1.12 min, chiral purity 100%.

Example 182: synthesis of (((18'R,E)-3',4'-difluoro-11',13'-dioxo-18'-phenyl-11',13'-dihydro-6'H,18'H-spiro[cyclobutane-1,9'-[10,17]methanobenzo[b]pyrido[1,2-f][1]oxa[5,6,9]triazacyclotridecin]-12'-yl)oxy)methyl methyl carbonate (Compound **182**)



Synthesis of compound 182:

25 To a solution of compound **146A** (161 mg, 0.328 mmol) in dry CH₃CN (2.1 mL) were added a solution of iodomethyl methyl carbonate [CAS 69862-08-4] (177 mg, 0.8 mmol) in dry CH₃CN (1.4 mL) and DBU (0.122 mL, 0.82 mmol). The reaction mixture was stirred for 19h at rt, was diluted with AcOEt and then washed with H₂O, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure.

30 The residue was purified by flash column chromatography over silica (40g, Eluent: CH₂Cl₂/MeOH 0 to 10%). The compound was purified again over silica (40g, Eluent:

CH₂Cl₂/MeOH 0 to 10%). The compound was purified again over silica (C18 12 g (eluent H₂O/MeOH 50:50 to 0:100) to give compound **182** (98 mg).

Compound 182:

5 ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.59 (m, 1H), 7.20 – 7.09 (m, 4H), 7.01 (d, *J* = 3.7 Hz, 2H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.41 (brs, 1H), 6.09 (brs, 1H), 5.96 (d, *J* = 6.4 Hz, 1H), 5.76 (d, *J* = 7.8 Hz, 1H), 5.75 (d, *J* = 6.4 Hz, 1H), 5.28 (s, 1H), 4.85 (d, *J* = 13.9 Hz, 1H), 4.76 – 4.66 (m, 1H), 4.59 (brs, 1H), 3.89 (d, *J* = 13.9 Hz, 1H), 3.87 (s, 3H) 2.84 (dd, *J* = 21.5, 10.7 Hz, 1H), 2.68 – 2.53 (m, 1H), 2.06 – 1.91 (m, 2H), 1.84
10 (dt, *J* = 17.5, 5.9 Hz, 1H), 1.78 – 1.62 (m, 1H).

LC/MS (method LC-oxeltis standard): Rt 3.34 min, MH⁺ 580

Chiral SFC (method SFC-C): Rt 1.15 min, chiral purity 100%.

Antiviral activity

15

EXAMPLE A

Influenza Antiviral Assay

Human lung carcinoma A549 cells (ATCC, Manassas, VA) were plated at a density of 5
20 x 10⁴ cells/mL (10 x 10³ cells/well) in assay media (Ham's F12 media supplemented with 0.3% FBS, 1% penicillin/streptomycin, 1% L-Glutamine, and 1% non-essential amino acids (all Mediatech, Manassas, VA) and 1% DMSO (Sigma-Aldrich, St Louis, MO)) in white 96-well plates. Cells were infected with 250 IU/well of Influenza strain A549 A/WSN/33 (H1N1) (Virapur, San Diego CA) and incubated for 20 hours at 37°C, 5%
25 CO₂. The cell culture supernatant was aspirated off and 50 µL of 25 µM 2'-(4-Methylumbelliferyl)-α-D-N-acetylneuraminic acid (Sigma-Aldrich) dissolved in 33 mM MES, pH 6.5 (Emerald Biosystems, Bainbridge Island, WA) was added to the cells. After incubation for 45 min at 37°C, reactions were stopped by addition of 150 µL stop solution (100 mM glycine, pH 10.5, 25% ethanol, all Sigma-Aldrich). Fluorescence was
30 measured with excitation and emission filters of 355 and 460 nm, respectively, on a Victor X3 multi-label plate reader (Perkin Elmer, Waltham, MA). Cytotoxicity of uninfected parallel cultures was determined by addition of 100 µL of CellTiter-Glo® reagent (Promega, Madison, WI), and incubation for 10 min at RT. Luminescence was measured on a Victor X3 multi-label plate reader.

35

EXAMPLE B

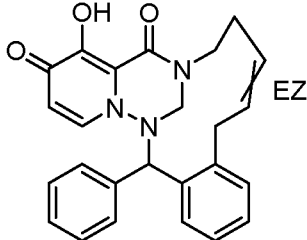
EN PA FRET Inhibition Assay

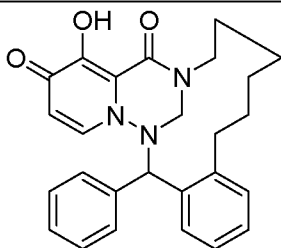
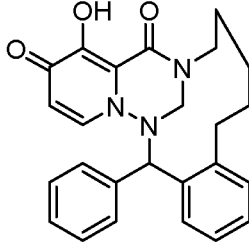
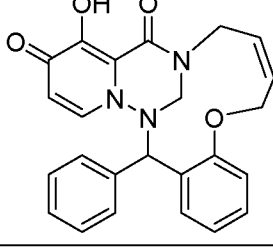
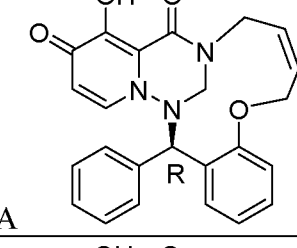
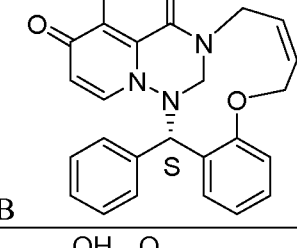
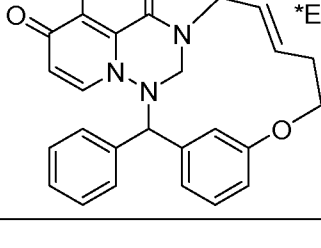
[0250] EN PA FRET inhibition assay was performed using a 19 nucleotide synthetic oligoribonucleotide substrate: 5'-FAM-AUUUUGUUUUUAAUAUUUC-BHQ-3' (Integrated DNA Technologies, Inc., Coralville, IA) (SEQ. ID. NO. 1). Upon RNA cleavage, the fluorescent FAM group is released from the BHQ quencher. The PA sequence used to produce active enzyme is derived from any one of multiple influenza A virus strains (e.g., A/goose/Nanchang/3-120/01 (H3N2), A/Victoria/3/1975 (H3N2), A/Brisbane/10/2007 (H3N2), A/WSN/33 (H1N1), A/CA/4/2009 (H1N1), A/CA/5/2009 (H1N1), A/Shanghai/1/2013 (H7N9), A/Guizhou/1/2009 (H5N1)). The full length recombinant protein was expressed from a baculovirus vector in insect cells. Full length EN PA was used in this assay at an effective concentration of 1 to 10 nM, together with 50 nM FRET probe with a final volume of 20 ml cleavage buffer (20 mM Tris Ph8, 100 mM NaCl, 5% Glycerol, 10 mM β -ME, 0.0003% Tween-20, 5 mM $MgCl_2$).

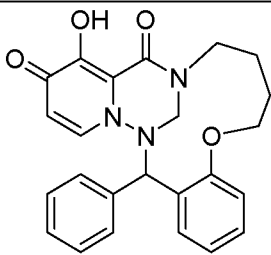
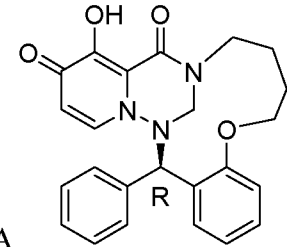
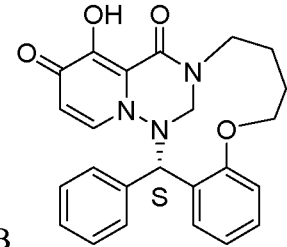
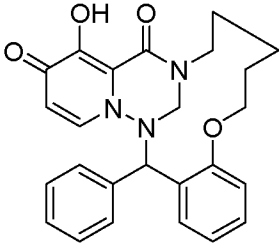
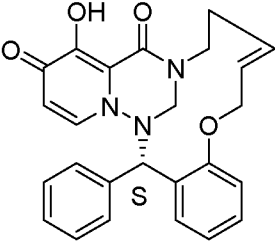
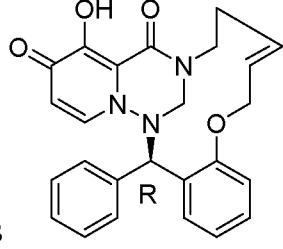
[0251] Compounds described herein were added to a 384-well black polypropylene plate. Fluorescence was measured in a continuous mode up to 120 minutes with a Wallac 1420 Victor³V multilabel counter (PerkinElmer Life Sciences, Shelton, CT) (excitation 485 nm; emission 535 nm). Measured IC_{50} is defined as the concentration at which fluorescence is 50% that of the uninhibited control (DMSO). IC_{50} was calculated by fitting the data to the sigmoidal equation $Y = \% \text{ Min} + (\% \text{ Max} - \% \text{ Min}) / (1 + X / IC_{50})$, where Y corresponds to the percent relative enzyme activity, Max is the maximum enzyme activity in the presence of DMSO, Min is the inhibited activity at saturating concentration of compound, and X corresponds to the compound concentration. The IC_{50} values were derived from the mean of a minimum of two independent experiments.

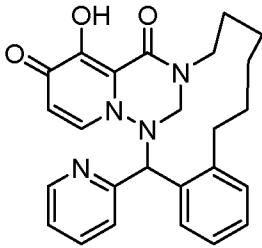
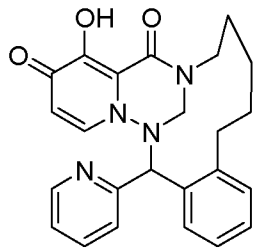
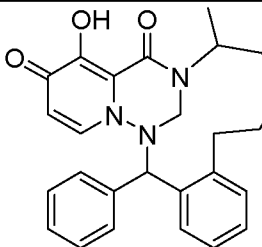
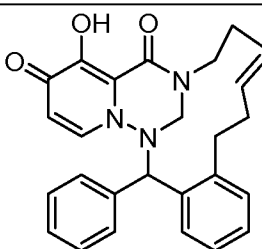
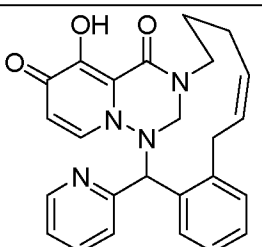
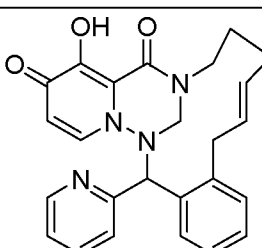
Table 1A shows the antiviral data obtained against influenza A H1N1 strain and cellular toxicity.

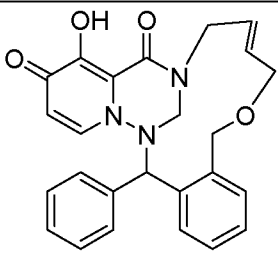
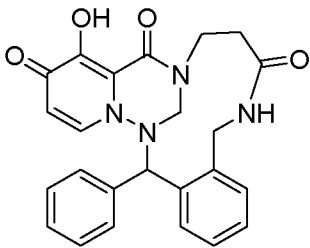
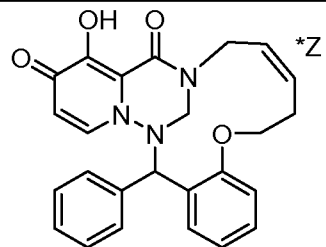
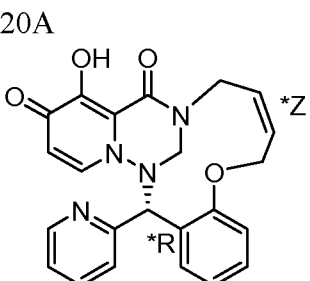
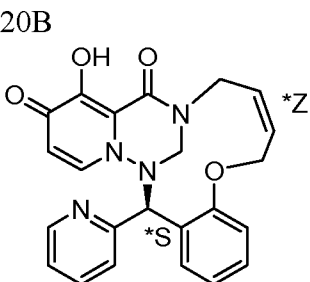
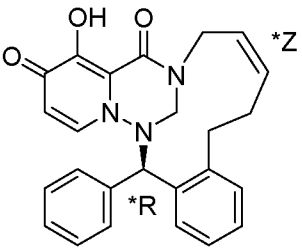
TABLE 1A. Antiviral activity of selected compounds (cell based and enzymatic assays)

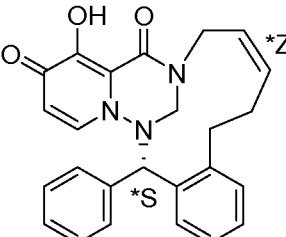
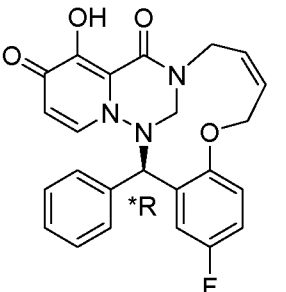
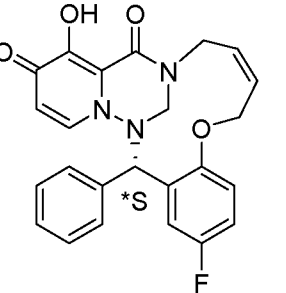
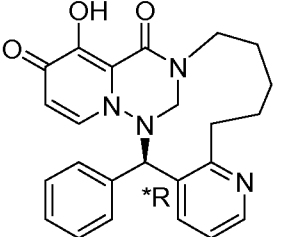
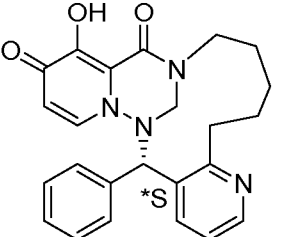
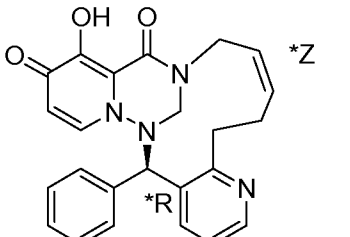
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μ M)	FRET_ _IC ₅₀ (uM)
 1	0.043	>2	0.069

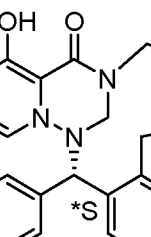
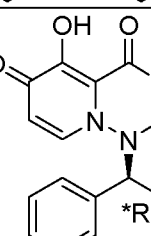
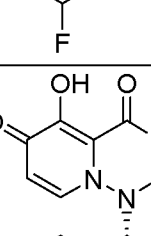
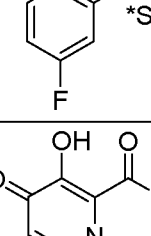
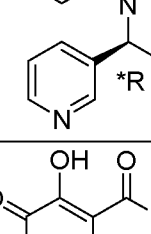
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
2 	0.354	>20	0.106
4 	0.048	>4	0.049
5 	0.026	>2	0.114
5A 	0.008	>2	0.050
5B 	>1	>2	0.311
6 	6.149	>20	0.278

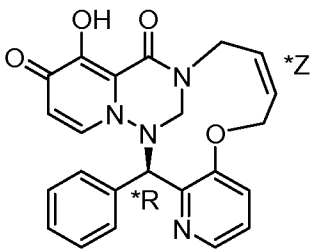
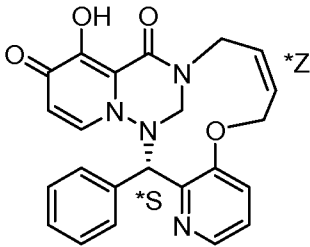
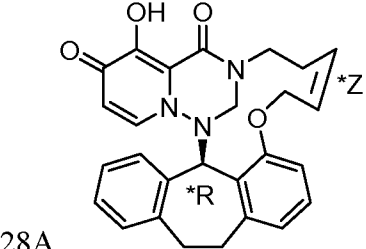
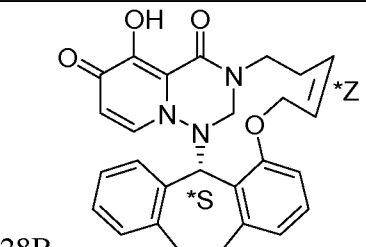
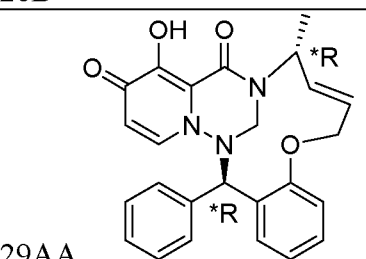
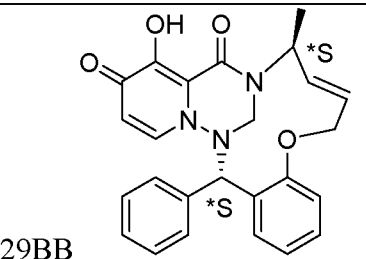
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
8 	0.059	>2	0.048
8A 	0.013	>2	0.038
8B 	4.129	>2	0.973
9 	0.453	>2	0.076
10A 	>1	>2	0.179
10B 	0.013	>2	0.047

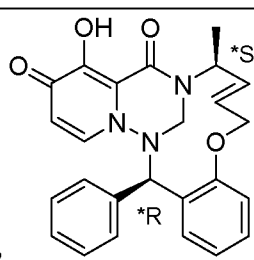
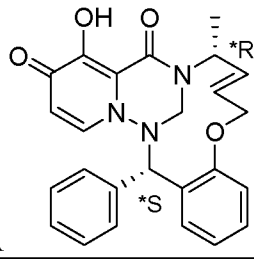
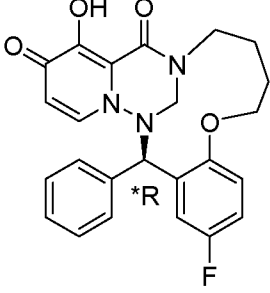
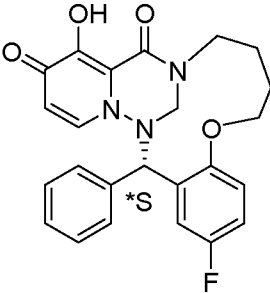
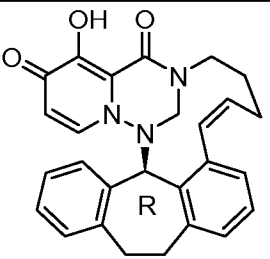
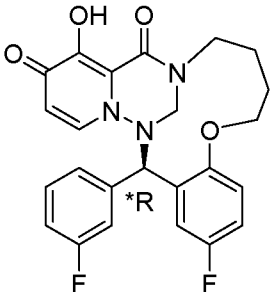
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
11 	0.363	>2	0.100
12 	0.086	>2	0.049
13 	0.019	>2	0.046
14 	0.048	>4	0.067
15 	0.635	>20	0.118
16 	0.142	>20	0.047

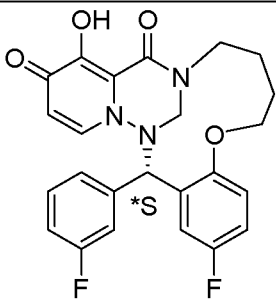
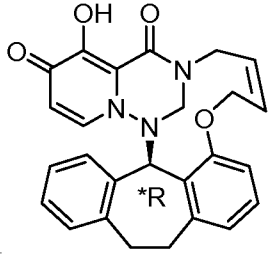
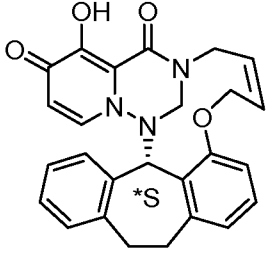
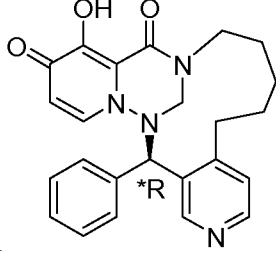
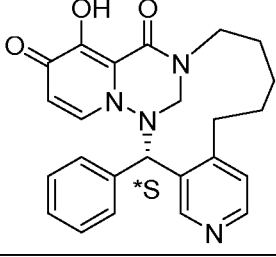
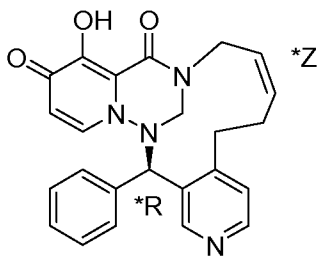
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
17 	0.077	>20	0.098
18 	7.907	>200	0.231
19 	0.260	>2	0.093
20A 	0.093	>2	0.030
20B 	10.024	>2	0.686
21A 	0.005	>1	0.036

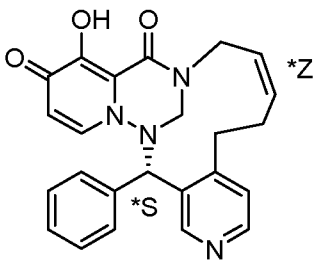
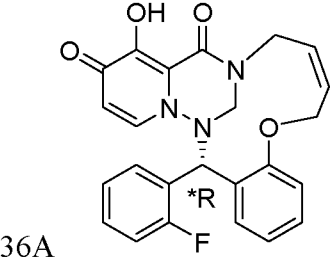
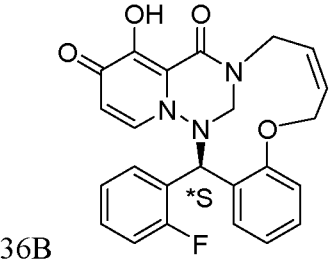
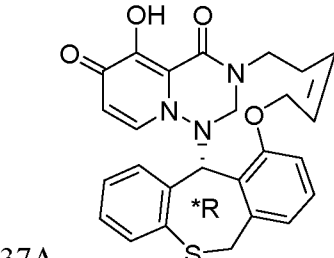
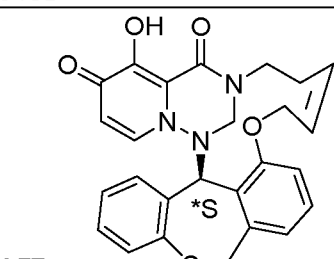
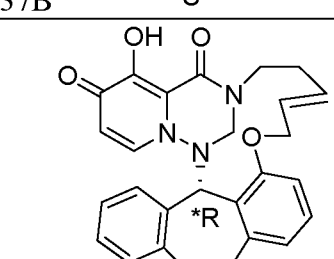
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
21B 	0.815	>1	0.128
22A 	9.540	>1	0.322
22B 	0.012	>1	0.043
23A 	54.987	>10	2.363
23B 	12.183	>1	0.240
24A 	39.591	>10	1.822

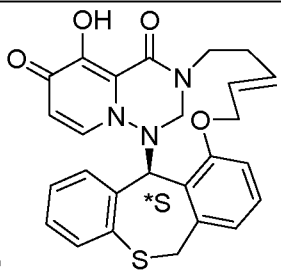
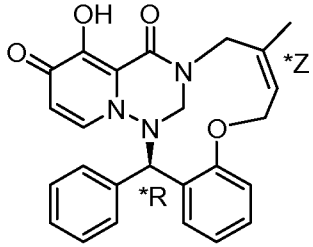
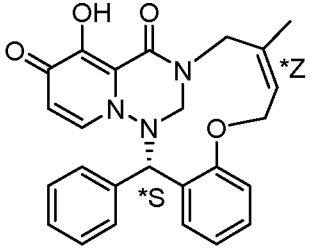
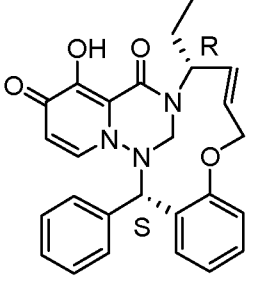
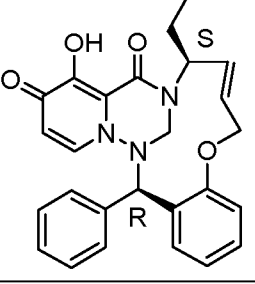
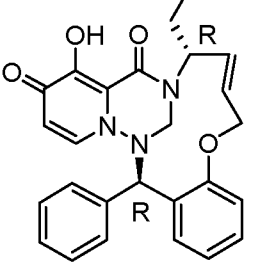
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
24B 	1.526	>1	0.233
25A 	9.799	>2	0.318
25B 	0.011	>2	0.041
26A 	0.394	>2	0.081
26B 	40.095	>4	0.606

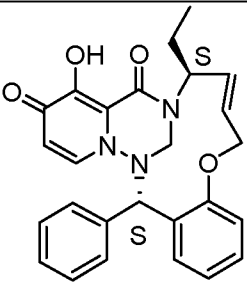
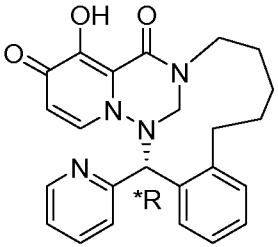
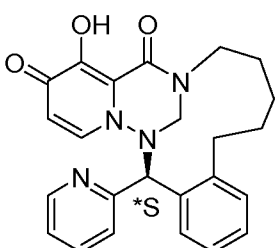
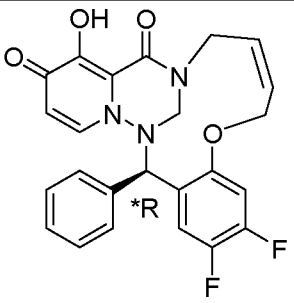
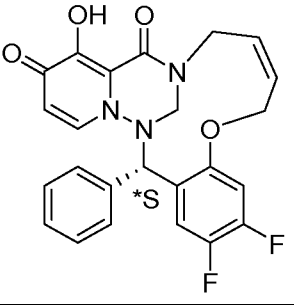
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
27A 	0.094	>2	0.052
27B 	45.736	>20	1.874
28A 	5.95	>20	5.78
28B 	0.006	>0.4	0.034
29AA 	>3	>2	1.437
29BB 	0.008	>2	0.071

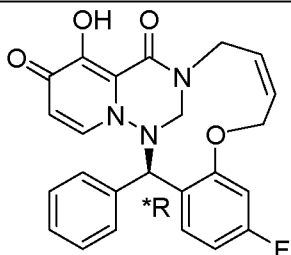
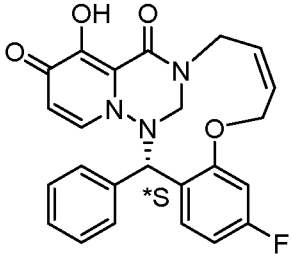
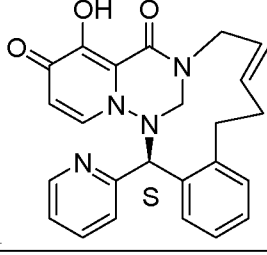
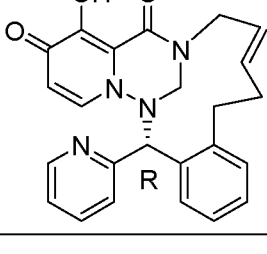
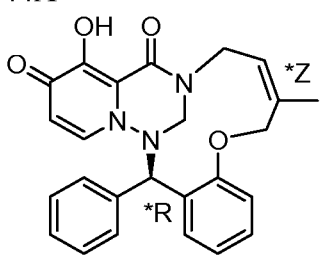
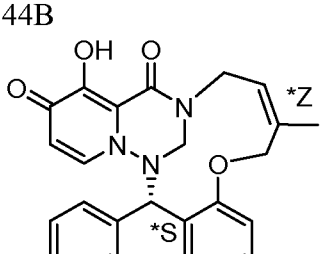
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM
29AB 	0.0057	>0.2	0.032
29BA 	1.714	83.06	2.213
30A 	>1	>2	3.114
30B 	0.015	>2	0.030
31B 	0.004	>2	0.007
32A 	>1	>2	2.320

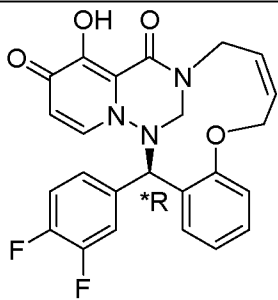
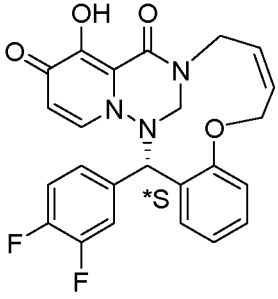
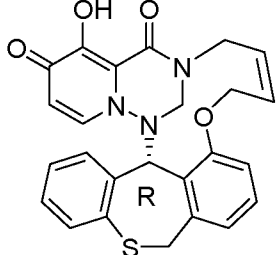
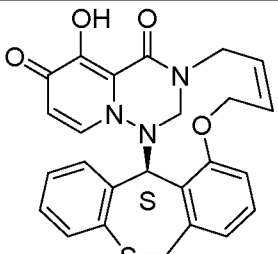
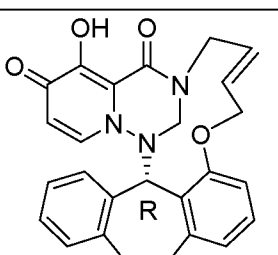
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
32B 	0.025	>2	0.058
33A 	>1	>2	0.373
33B 	0.015	>2	0.018
34A 	0.059	>2	0.037
34B 	>1	>2	1.048
35A 	0.069	>2	0.039

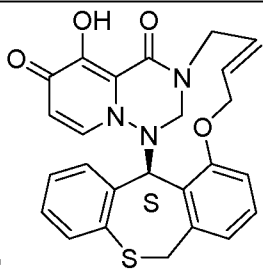
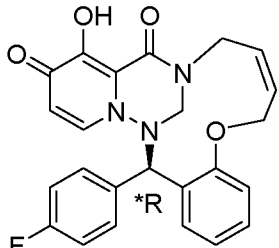
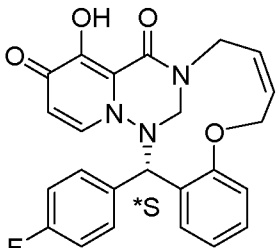
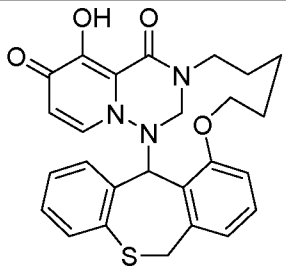
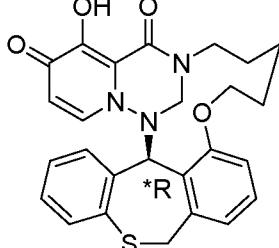
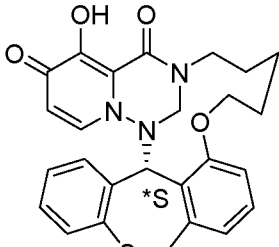
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
35B 	>1	>2	0.782
36A 	0.015	>2	0.035
36B 	0.815	>2	0.472
37A 	12.200	>2	2.931
37B 	0.004	>0.2	0.024
37C 	>1	>2	ND

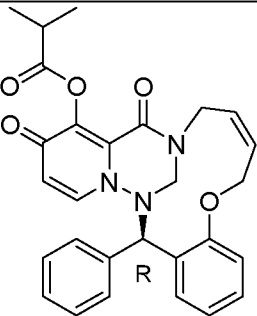
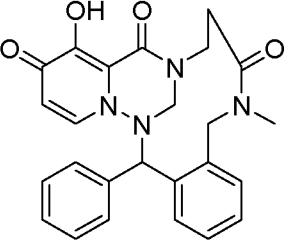
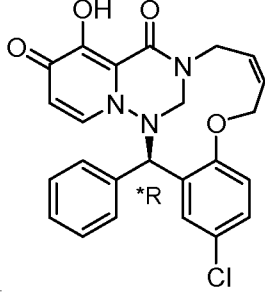
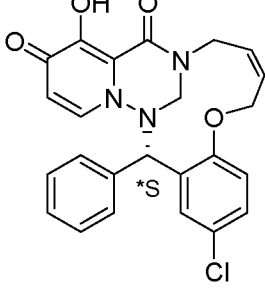
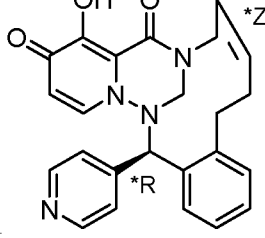
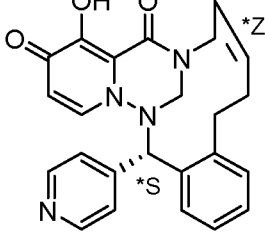
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
37D 	0.001	>0.2	ND
38A 	>1	>2	2.332
38B 	0.026	>2	0.058
39AA 	>1	>2	37.432
39BB 	0.007	>2	0.065
39BA 	0.006	>0.2	0.049

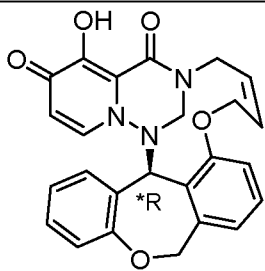
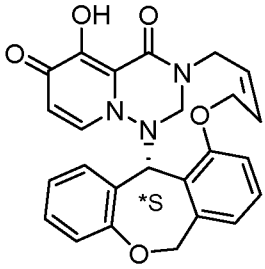
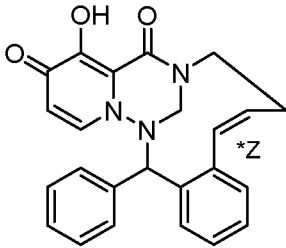
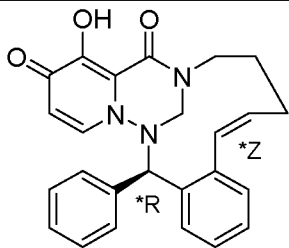
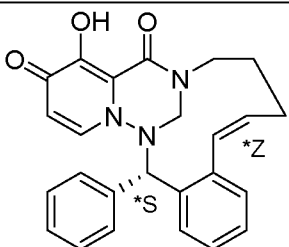
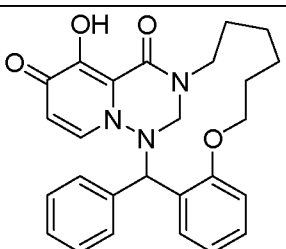
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
39AB 	>1	>2	25.0
40A 	0.030	>2	0.027
40B 	>1	>2	0.937
41A 	0.294	>2	0.263
41B 	0.006	>2	0.031

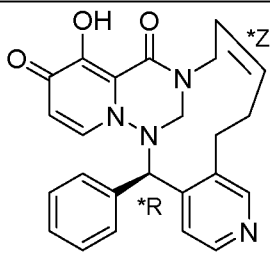
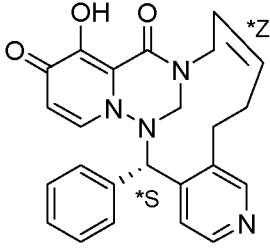
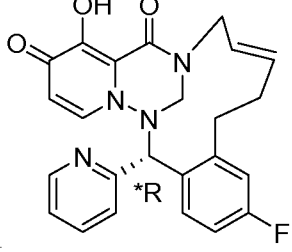
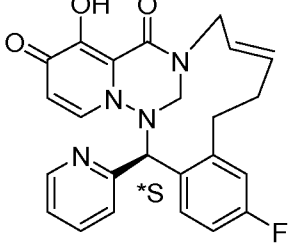
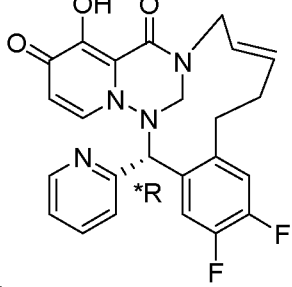
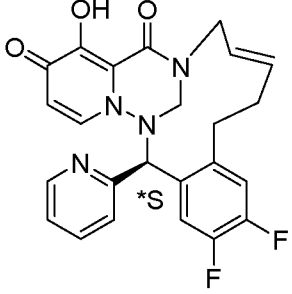
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
42A 	>1	>2	0.548
42B 	0.006	>2	0.018
43A 	0.022	>2	0.024
43B 	>1	>2	1.319
44A 	>0.1	>0.2	0.037
44B 	>10	>20	8.846

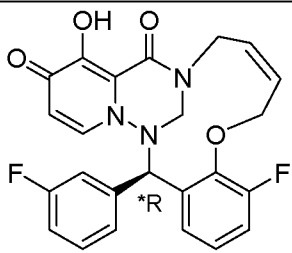
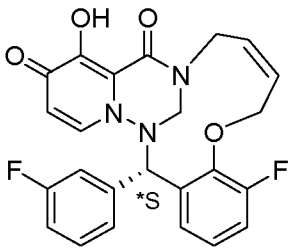
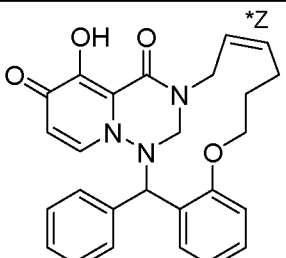
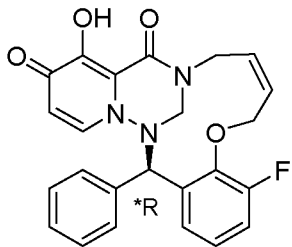
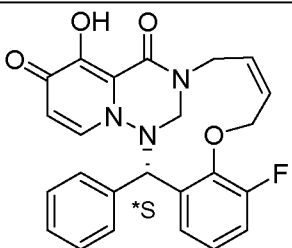
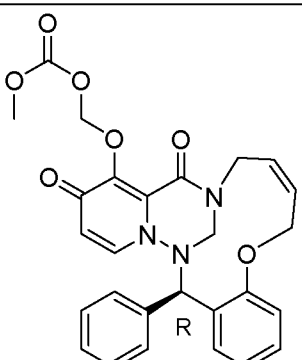
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
 45A	>1	>2	0.681
 45B	0.014	>0.2	0.023
 46A	0.064	>2	0.221
 46B	0.003	>0.1	0.003
 46C	0.33	>2	0.21

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
46D 	0.001	>0.2	0.011
47A 	>1	>2	1.511
47B 	0.015	>0.2	0.029
48 	0.032	>2	0.052
48A 	>1	>2	1.63
48B 	0.027	>2	0.021

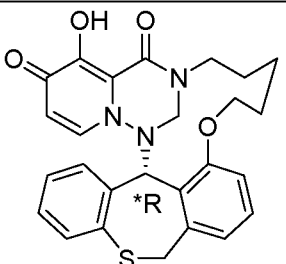
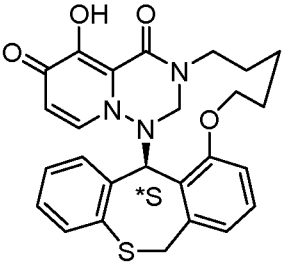
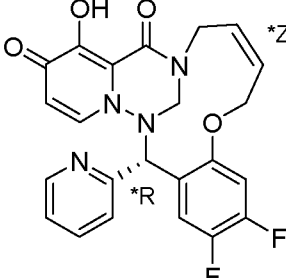
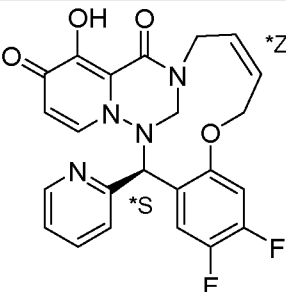
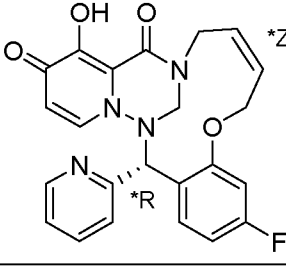
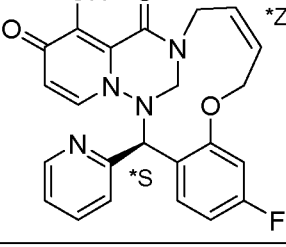
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
49 	prodrug		
50 	>1	>2	0.164
51A 	>1	>2	2.56
51B 	0.010	>2	0.053
52A 	>1	>2	0.653
52B 	0.084	>2	0.040

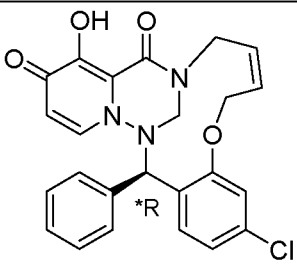
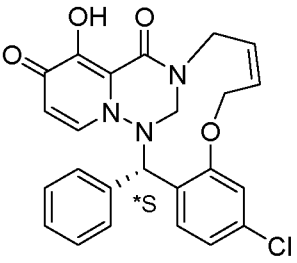
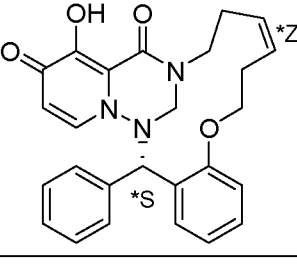
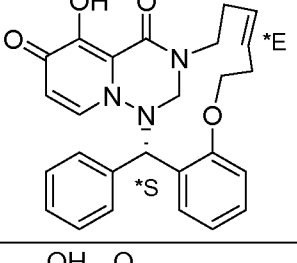
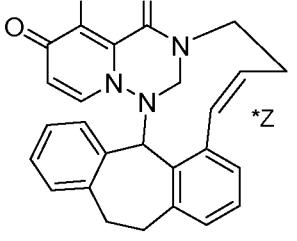
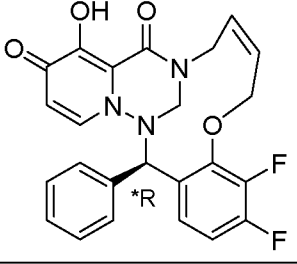
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
53A 	0.034	>2	0.025
53B 	>1	>2	54.178
54 	0.117	>20	0.012
54A 	>1	>2	0.266
54B 	0.033	>2	0.006
55 	0.880	>2	0.096

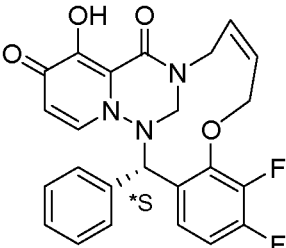
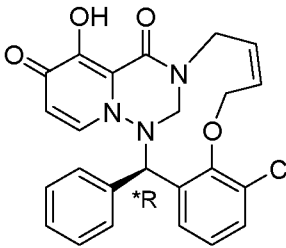
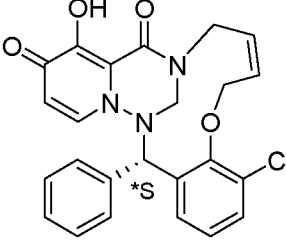
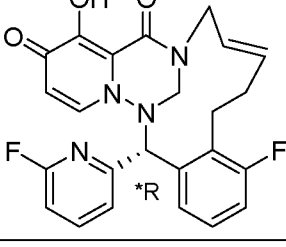
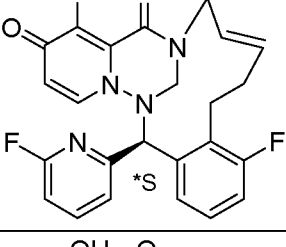
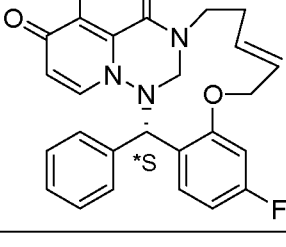
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
56A 	>1	>2	2.015
56B 	0.161	>2	0.125
57A 	0.032	>2	0.023
57B 	>1	>2	11.447
58A 	0.044	>2	0.049
58B 	>1	>2	12.233

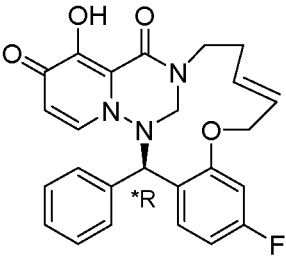
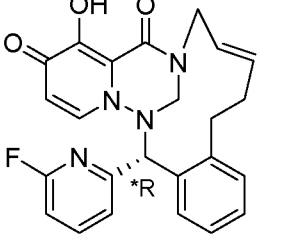
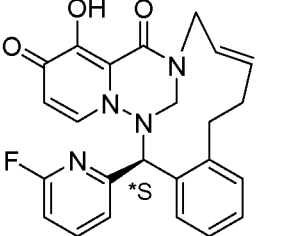
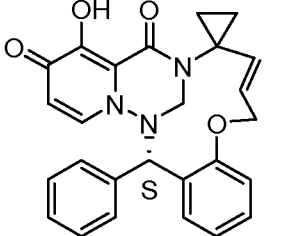
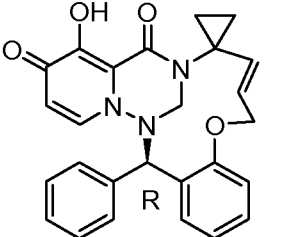
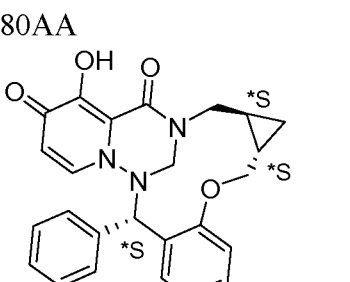
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
59A 	0.005		0.007
59B 	0.497	>2	0.207
60 	>1	>2	0.102
61A 	0.005	>2	0.008
61B 	0.155	>2	0.125
62 	prodrug		

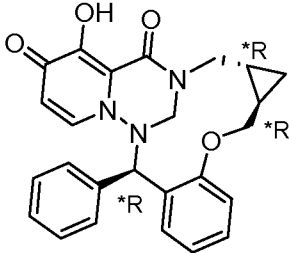
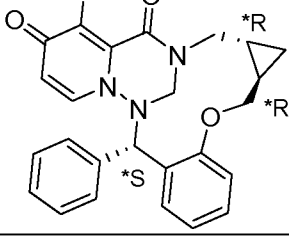
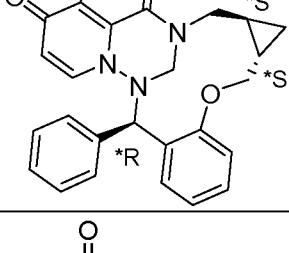
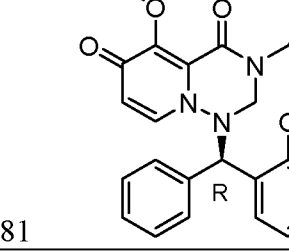
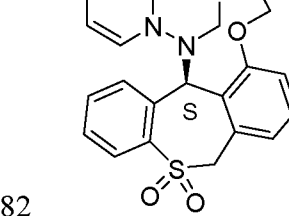
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
63A	>1	>2	0.398
63B	0.013	>2	0.024
65A	>5	>10	1.426
65C	7.889	>20	3.043
67A	>1	>2	5.706
67B	>1	>2	0.102

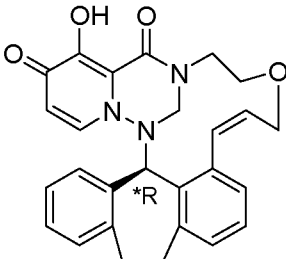
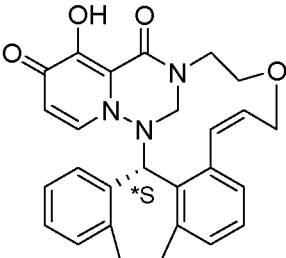
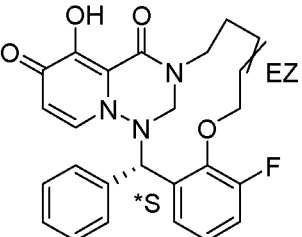
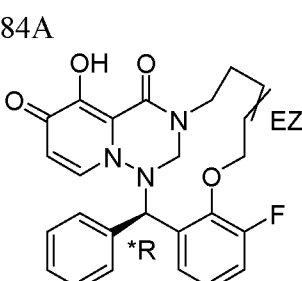
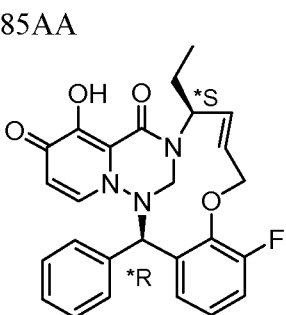
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM
69A 	>1	>2	1.63
69B 	0.027	>2	0.021
70A 	>10	>20	35.364
70B 	0.032	>0.2	0.054
71A 	0.034	>0.2	0.027
71B 	7.690	>20	1.582

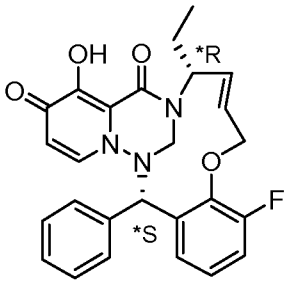
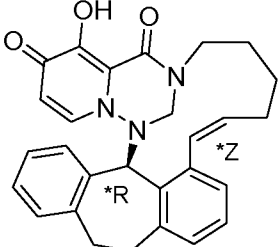
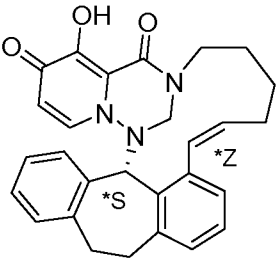
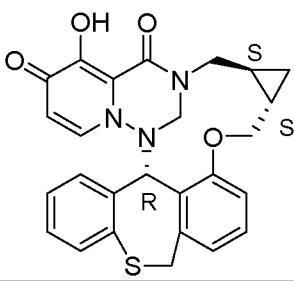
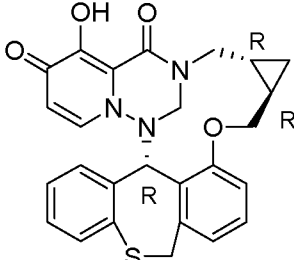
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
72A 	>1	>2	2.570
72B 	0.008	>2	0.028
65B 	0.047	>2	0.062
65D 	0.066	>2	0.097
73 	0.016	>2	0.008
74A 	>1	>2	0.825

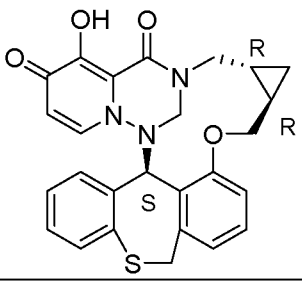
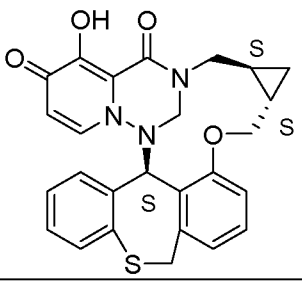
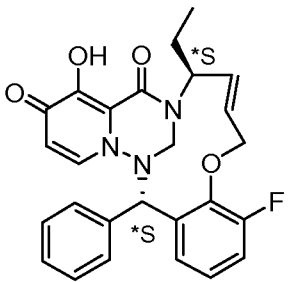
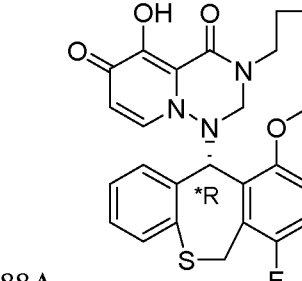
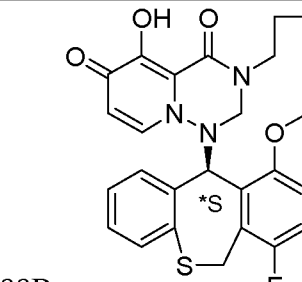
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
74B 	0.002	>0.2	0.006
75A 	0.269	>2	0.253
75B 	0.003	>0.2	0.011
76A 	3.589	43.87	0.346
76B 	0.006	>0.2	0.009
77A 	5.28	33.17	0.361

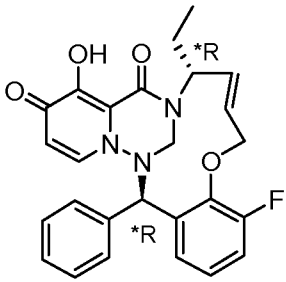
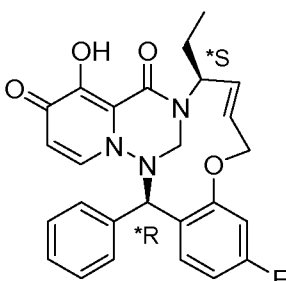
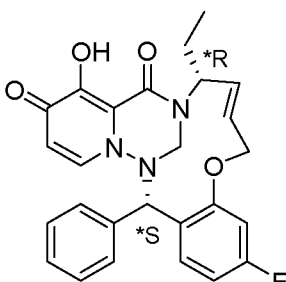
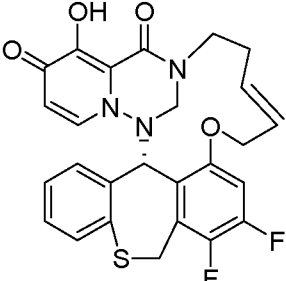
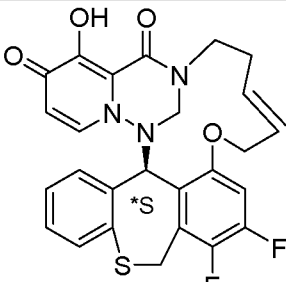
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM
77B 	0.012	>1	0.028
78A 	0.019	>1	0.044
78B 	6.430	61.62	0.817
79A 	>0.5	>1	2.511
79B 	0.006	>1	0.028
80AA 	0.167	>1	0.077

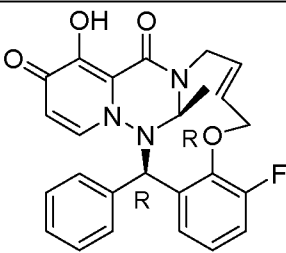
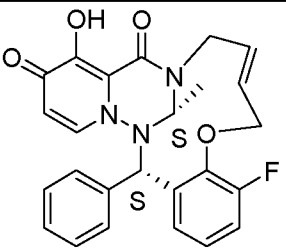
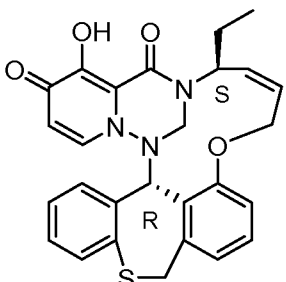
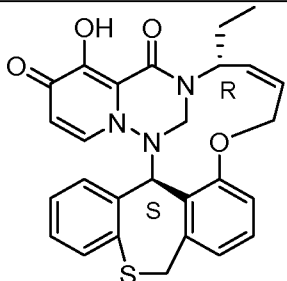
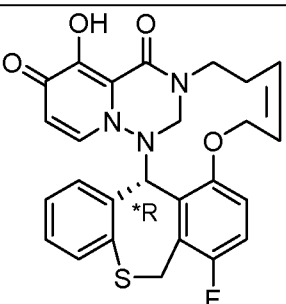
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
80BB 	>0.5	>1	0.670
80AB 	0.066	>10	0.028
80BA 	>0.5	>1	0.367
81 	prodrug		
82 	0.071	>1	0.014

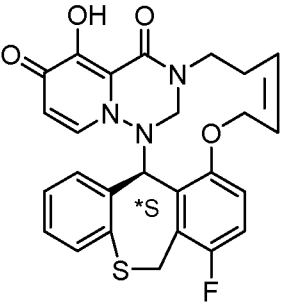
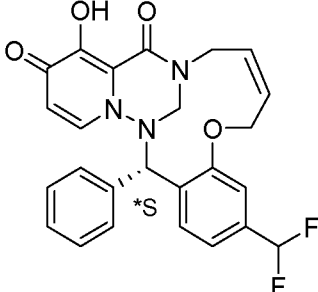
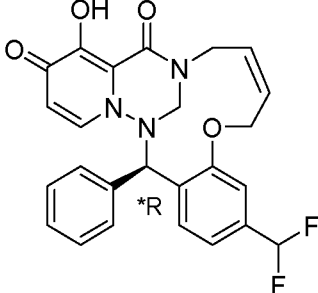
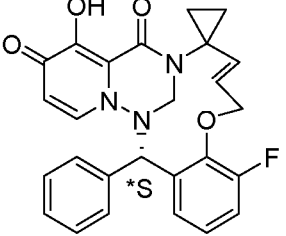
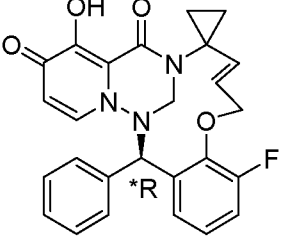
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
83A 	>0.5	>1	0.280
83B 	0.006	>0.2	0.017
84B 	0.005	>0.2	0.017
84A 	ND		0.428
85AA 	0.003	>0.2	0.017

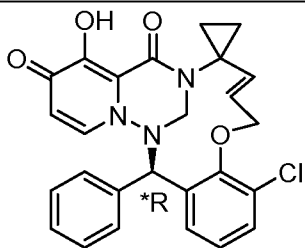
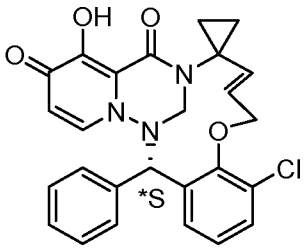
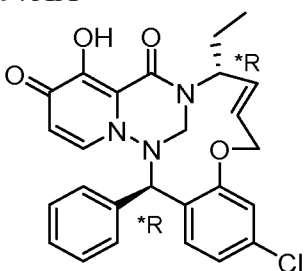
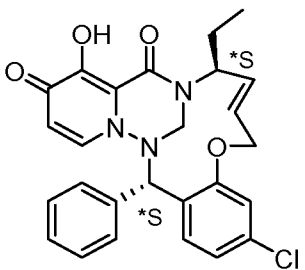
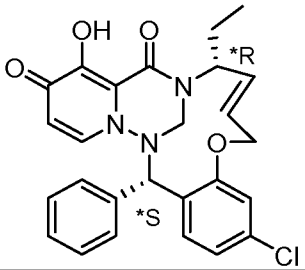
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
85BB 	ND	ND	0.902
86A 	ND	ND	6.411
86B 	0.027	>2	0.007
87AA 	ND	ND	2.375
87AB 	ND	ND	>100

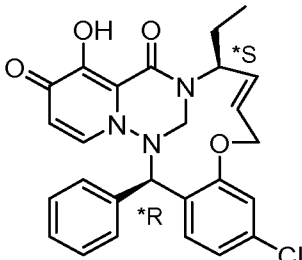
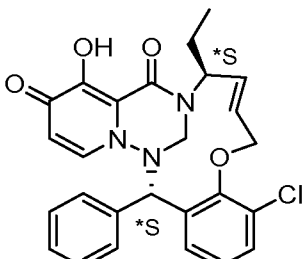
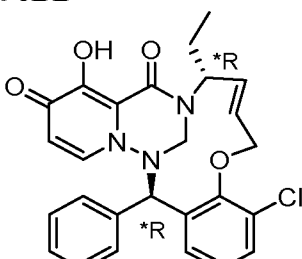
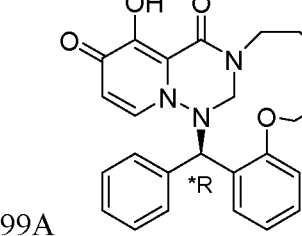
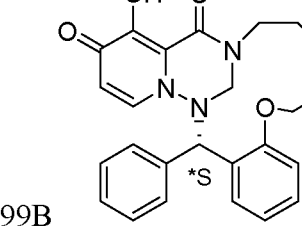
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
87BB 	0.004	>0.2	0.014
87BA 	0.004	>0.2	0.017
85BA 	>0.5	>1	>100
88A 	>0.5	>1	2.423
88B 	0.001	>0.2	0.006

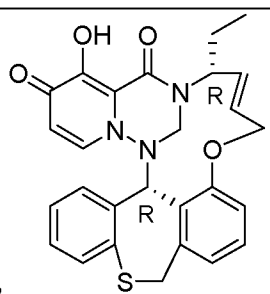
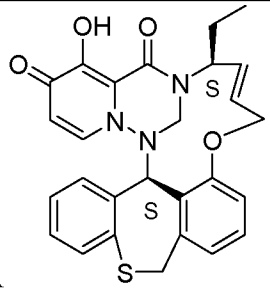
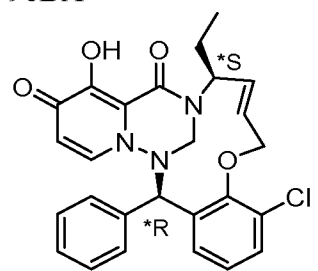
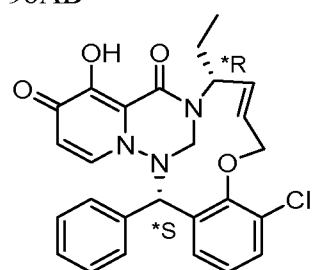
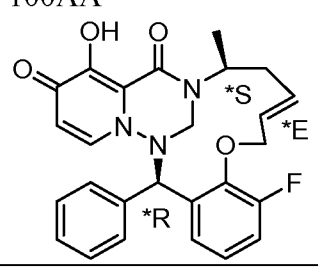
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
85AB 	0.002	>0.2	0.008
89AA 	10.820	39.28	>100
89BB 	0.003	>0.2	0.014
88C 	>0.5	>1	1.628
88D 	0.001	>0.1	0.006

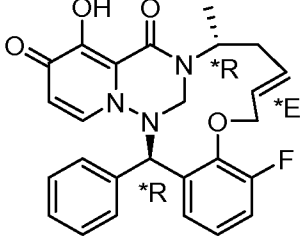
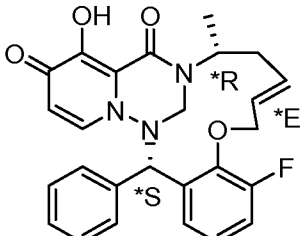
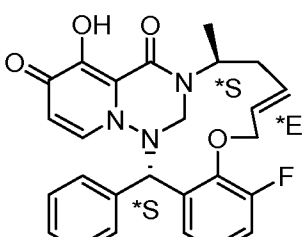
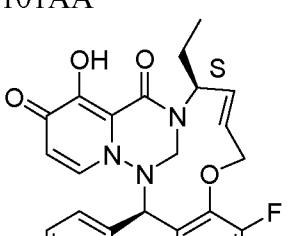
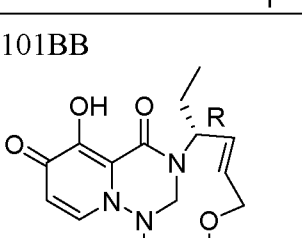
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
91A 	0.003	>1	0.009
91B 	>0.5	>1	0.617
92AA 	0.108	>1	0.340
92BB 	0.0015	>0.1	0.008
93A 	>0.5	>1	79.912

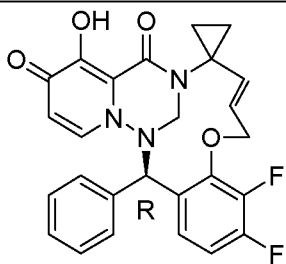
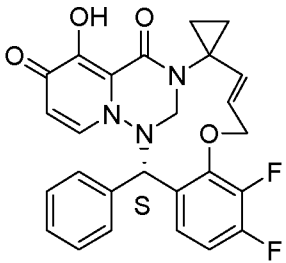
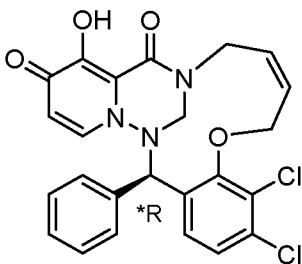
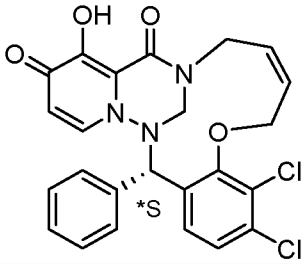
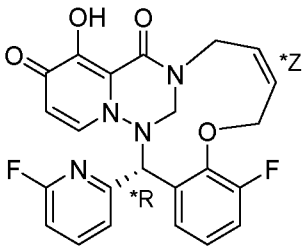
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
93B 	0.0022	>0.2	0.022
94A 	0.0257	>1	0.031
94B 	>0.5	>1	5.881
95A 	>0.5	>1	46.702
95B 	0.0017	>1	0.010

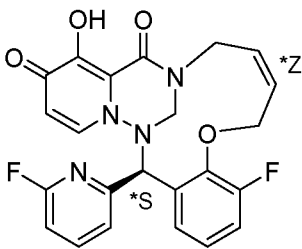
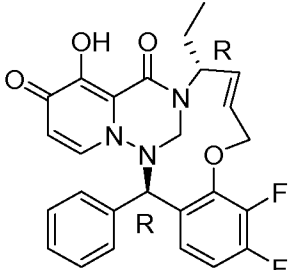
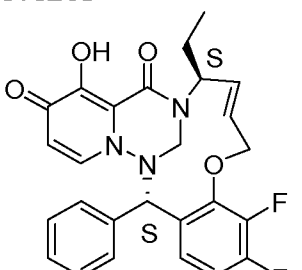
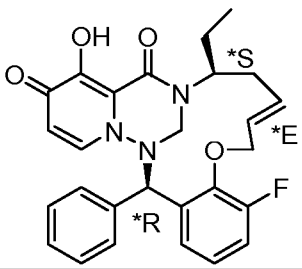
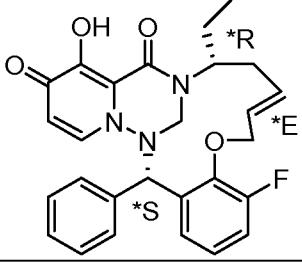
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
96A 	0.0019	>0.2	0.013
96B 	>0.5	>1	0.606
97AA 	0.0058	>1	0.020
97BB 	>0.5	>1	1.726
97BA 	>0.5	>1	37.160

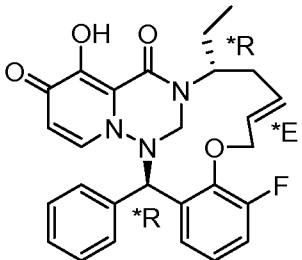
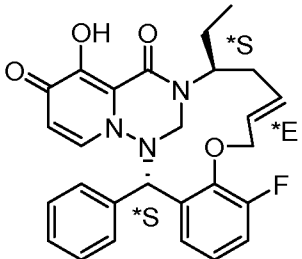
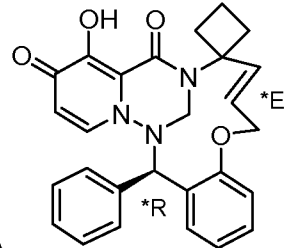
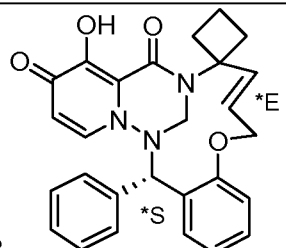
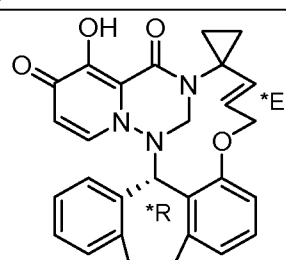
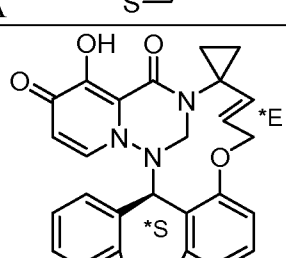
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
97AB 	0.0056	>1	0.023
98AA 	>0.5	>1	66.379
98BB 	0.0021	>1	0.017
99A 	>0.5	>1	0.376
99B 	0.1673	>1	0.102

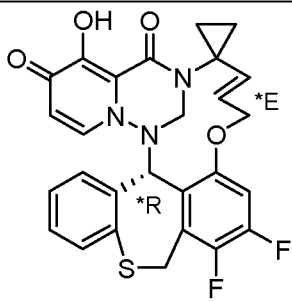
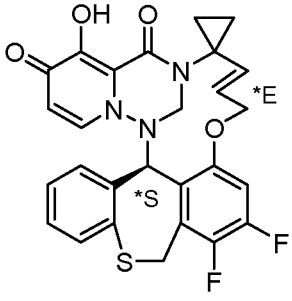
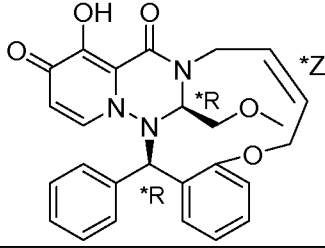
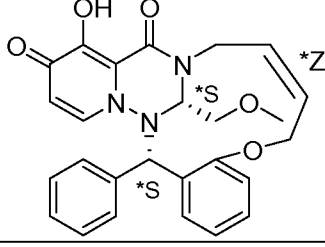
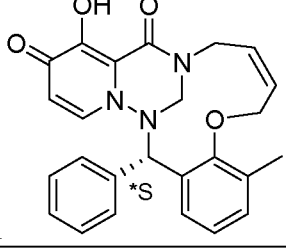
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
92AB 	>0.5	>1	5.779
92BA 	0.0007	ND	0.011
98BA 	0.830	26.45	9.782
98AB 	0.0022	>0.2	0.012
100AA 	0.0017	>0.1	0.003

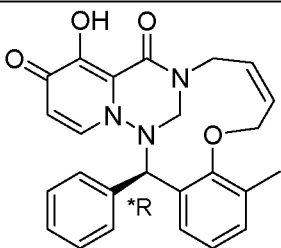
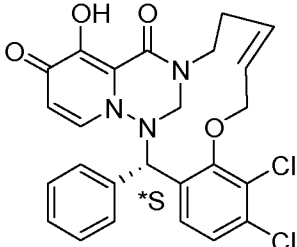
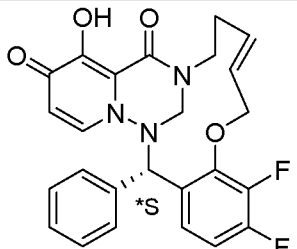
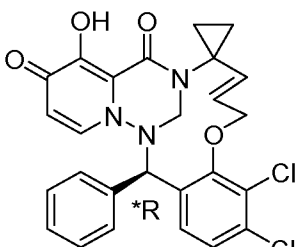
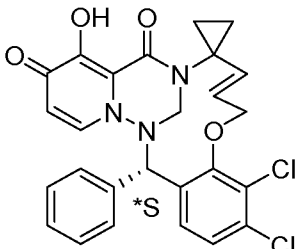
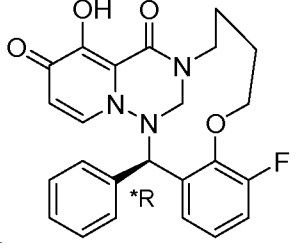
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
100AB 	0.0021	>0.2	0.010
100BB 	1.156	32.52	2.0
100BA 	5.214	40.21	10.267
101AA 	0.0007	>0.1	0.005
101BB 	5.031	29.89	>100

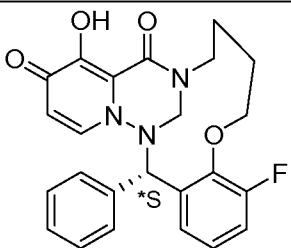
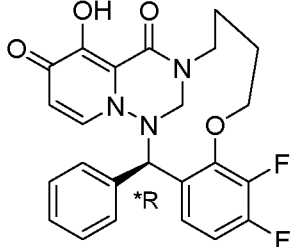
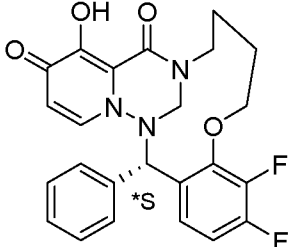
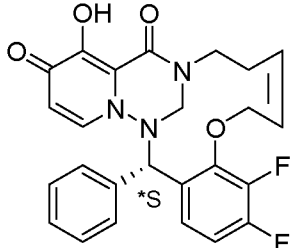
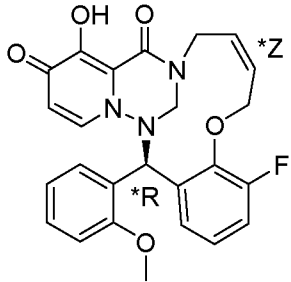
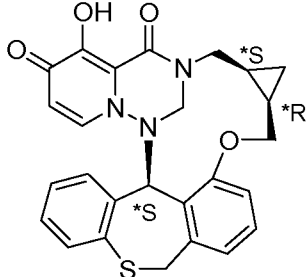
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
102A 	0.0009	>0.1	0.004
102B 	3.356	33.90	>100
103A 	>0.1	>0.2	71.210
103B 	0.0031	>0.2	0.009
104A 	0.0107	>0.2	0.012

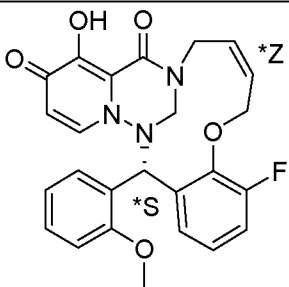
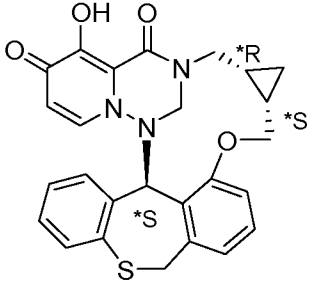
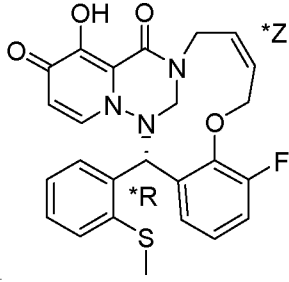
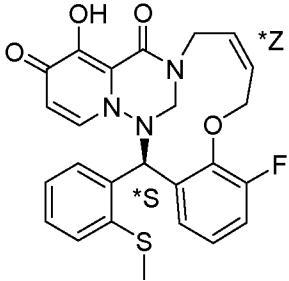
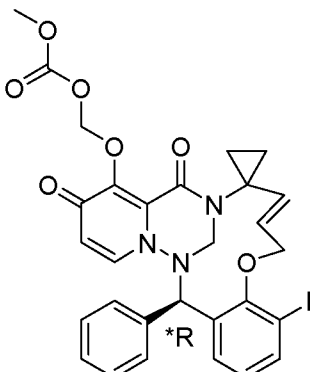
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
104B 	>0.1	>0.2	1.754
101AB 	0.0013	>0.2	0.006
101BA 	>0.1	>0.2	0.671
105AA 	0.0022	>0.2	0.010
105BB 	>0.1	>0.2	1.724

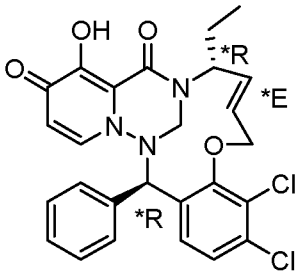
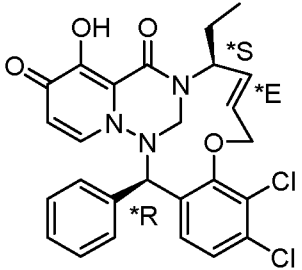
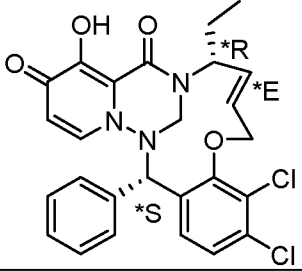
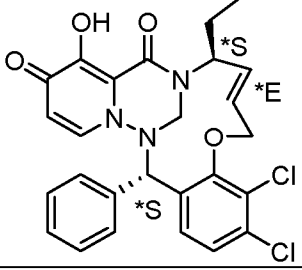
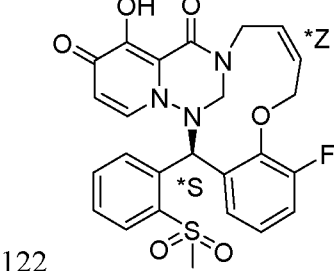
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
105AB 	0.0019	>0.2	0.010
105BA 	>0.1	>0.2	0.984
106A 	0.0035	>0.2	0.032
106B 	>0.1	>0.2	>100
107A 	>0.1	>0.2	74.981
107B 	0.001	>0.1	0.006

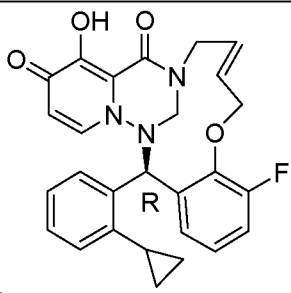
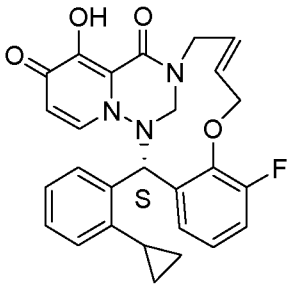
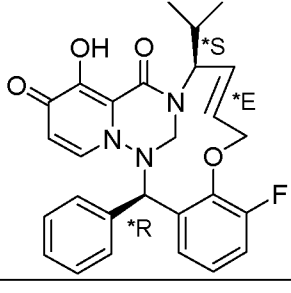
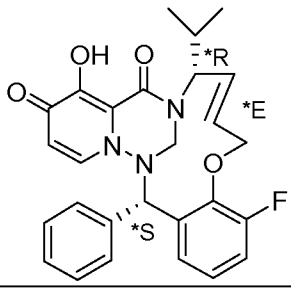
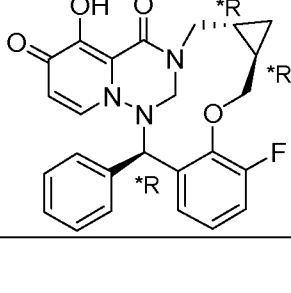
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
108A 	0.8395	22.60	3.733
108B 	0.0002	>0.05	0.002
109A 	0.0066	>0.2	0.033
109B 	>0.1	>0.2	0.68
110A 	0.0064	>0.2	0.024

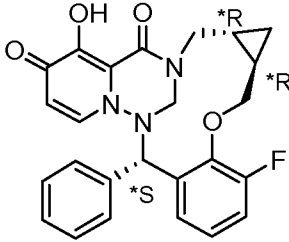
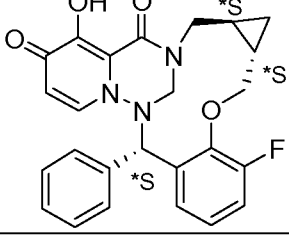
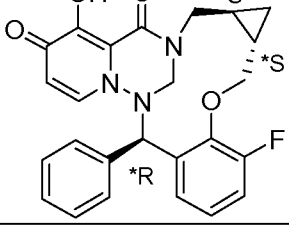
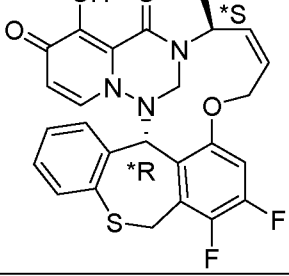
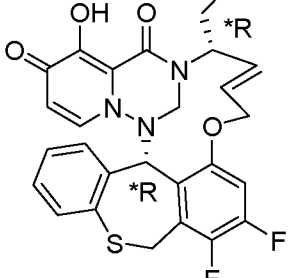
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
110B 	>0.1	>0.2	1.3
111A 	0.0043	>0.2	0.01
112A 	0.0038	>0.2	0.009
113A 	>0.1	>0.2	3.84
113B 	0.002	>0.2	0.008
114A 	0.007	>0.2	0.004

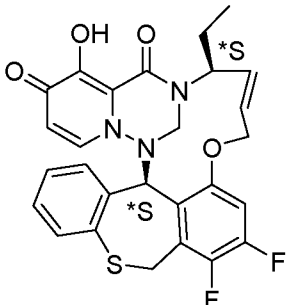
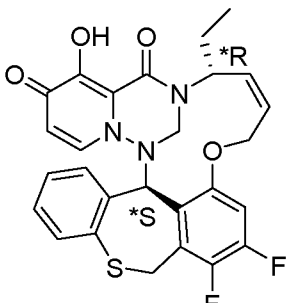
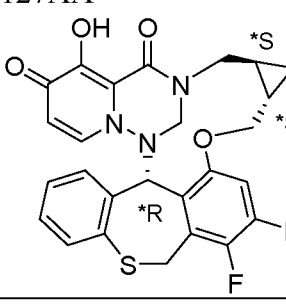
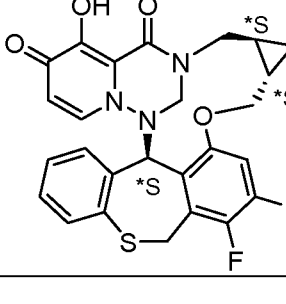
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
114B 	>0.1	>0.2	0.045
115A 	>0.1	>0.2	0.64
115B 	0.0044	>0.2	0.083
116A 	0.014	>0.2	0.004
117A 	0.029	>0.2	0.004
118AA 	0.0062	>0.2	0.020

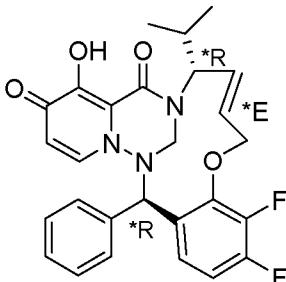
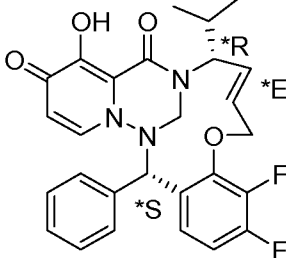
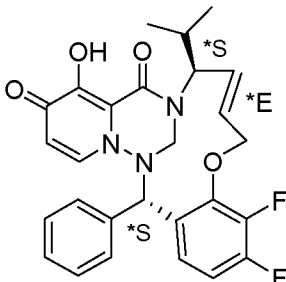
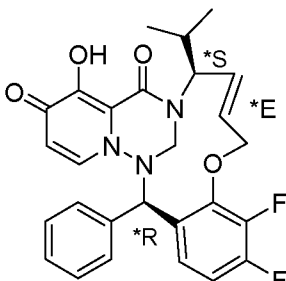
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
117B 	>0.1	>0.2	0.2
118AB 	0.010	>0.2	0.012
119A 	>0.1	>0.2	0.070
119B 	0.022	>0.2	0.002
120 	prodrug		

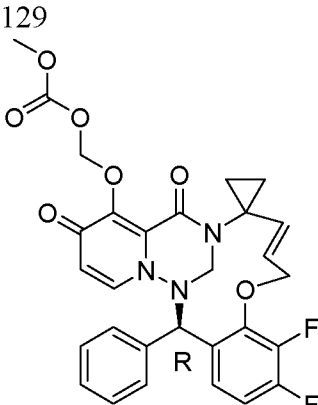
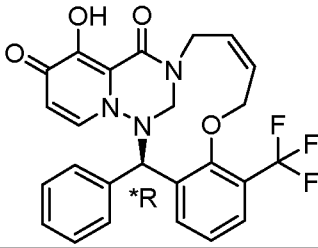
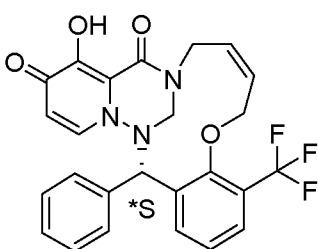
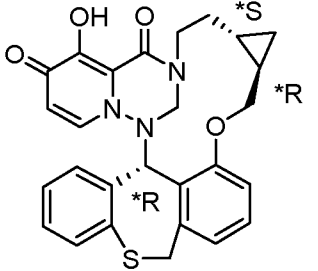
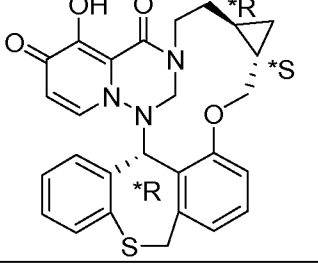
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
121AA 	0.0035	>0.2	0.011
121AB 	>0.1	>0.2	>100
121BA 	0.0028	>0.2	0.011
121BB 	0.060	>0.2	1.29
122 	>0.1	>0.2	10

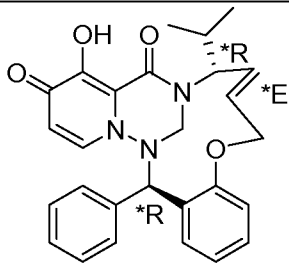
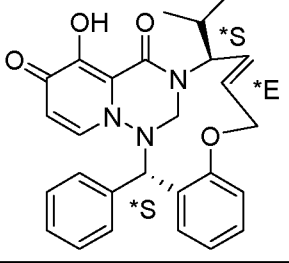
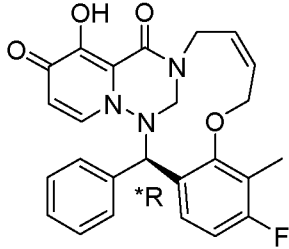
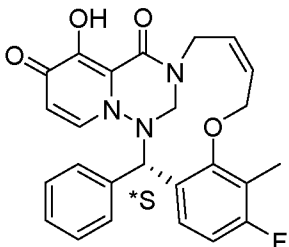
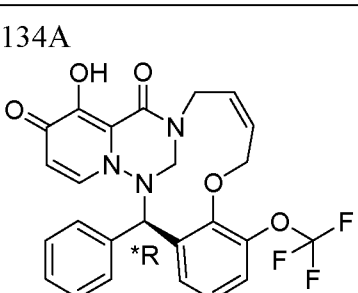
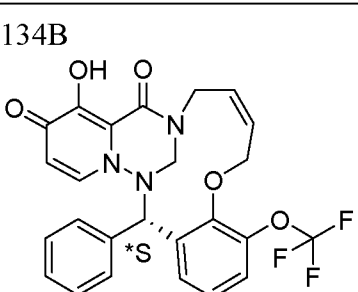
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
123A 	0.0029	>0.2	0.0004
123B 	>0.1	>0.2	>100
124AA 	>0.1	>0.2	ND
124BB 	0.0053	>0.2	0.018
125AA 	0.051	>0.2	0.016

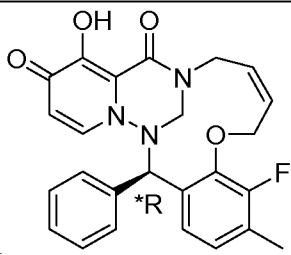
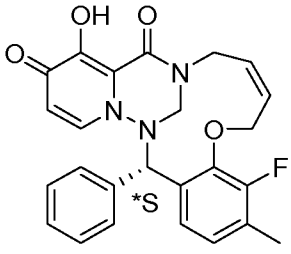
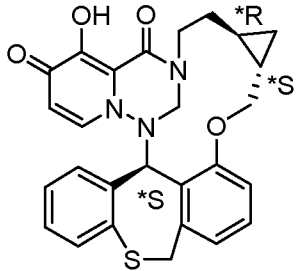
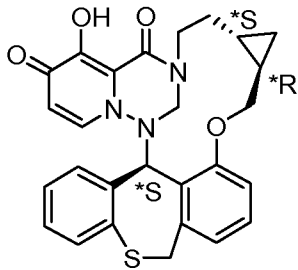
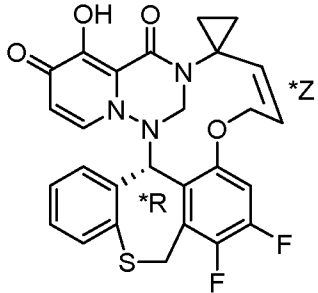
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
125BA 	>0.1	>0.2	0.18
125BB 	>0.1	>0.2	3.41
125AB 	0.024	>0.2	0.0096
126AA 	>0.1	>0.2	>50
126AB 	>0.1	>0.2	3.15

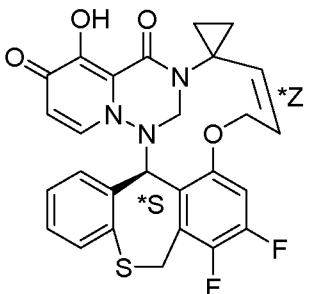
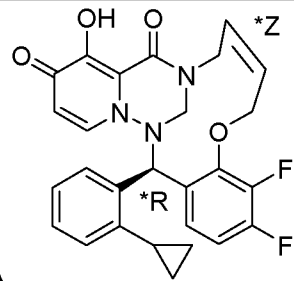
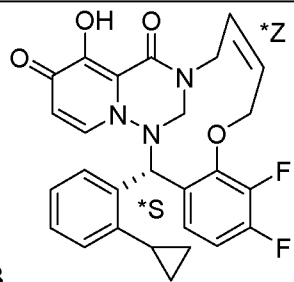
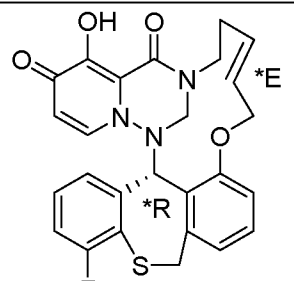
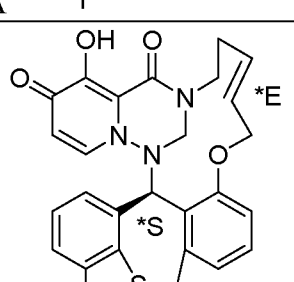
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
126BA 	0.00023	>0.05	0.0034
126BB 	0.001	>0.2	0.0024
127AA 	0.0015	>0.2	0.007
127BA 	0.0014	>0.2	0.006

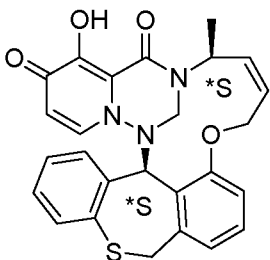
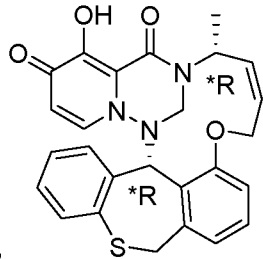
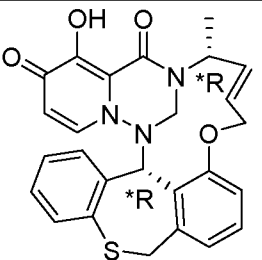
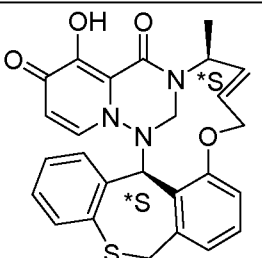
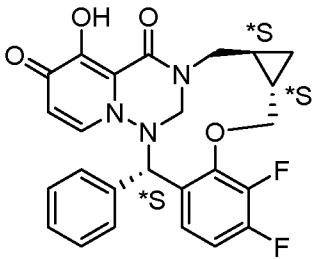
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
128AA 	>0.1	>0.2	46
128BA 	>0.1	>0.2	0.043
128BB 	0.0039	>0.2	0.008
128AB 	0.065	>0.2	0.093

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
129 	prodrug		
130A 	0.0048	>0.2	0.012
130B 	>0.1	>0.2	>100
131AA 	0.0047	>0.2	0.009
131AB 	0.017	>0.2	0.006

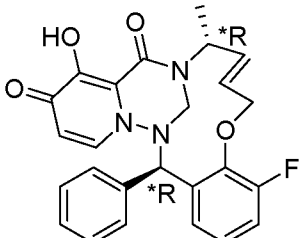
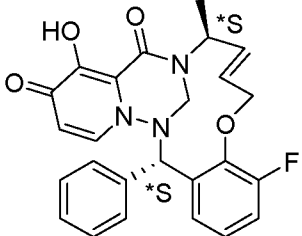
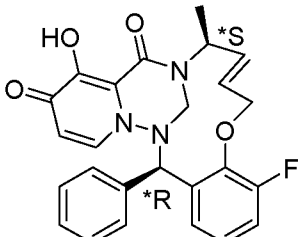
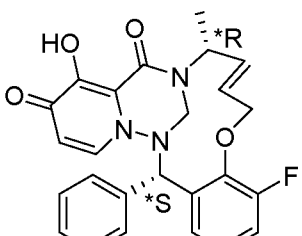
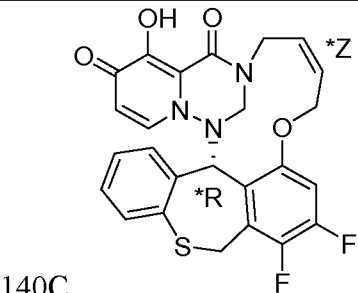
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
132A 	>0.1	>0.2	>100
132B 	0.0093	>0.2	0.064
133A 	0.0041	>0.2	0.035
133B 	>0.1	>0.2	2.523
134A 	0.0693	>0.2	0.059
134B 	>0.1	>0.2	>100

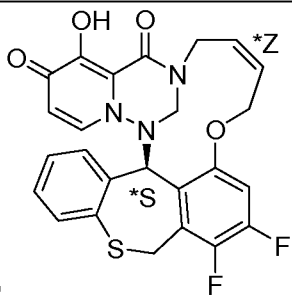
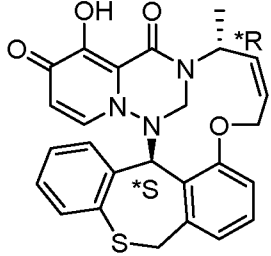
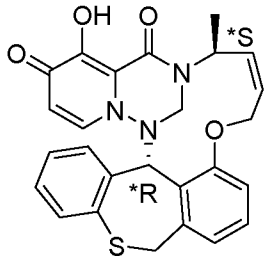
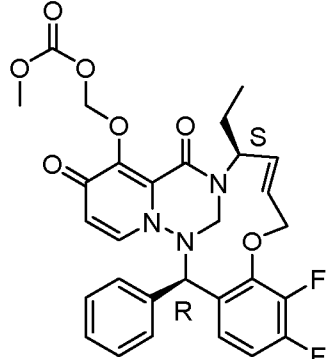
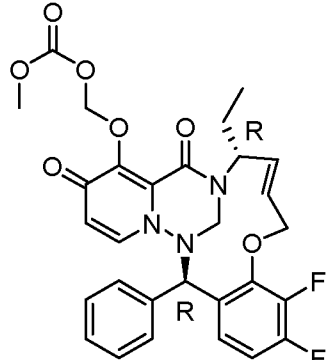
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
135A 	0.0073	>0.2	0.011
135B 	>0.1	>0.2	0.698
131BB 	>0.1	>0.2	0.851
131BA 	>0.1	>0.2	>100
108C 	>0.1	>0.2	2.388

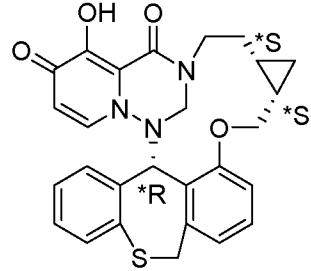
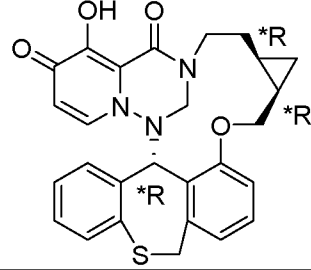
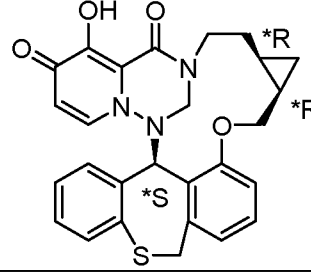
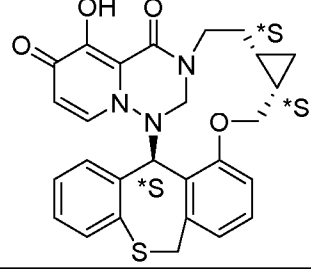
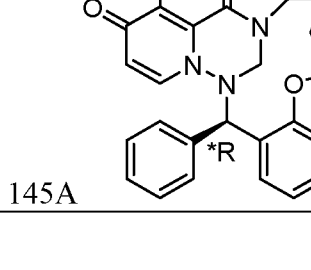
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
108D 	0.0009	>0.2	0.003
136A 	0.0063	>0.2	0.001
136B 	>0.1	>0.2	0.200
137A 	>0.1	>0.2	2.255
137B 	0.0053	>0.2	0.010

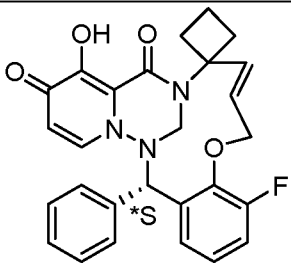
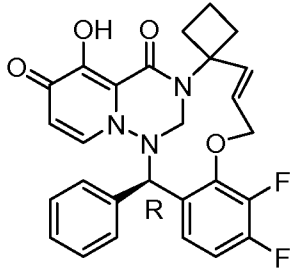
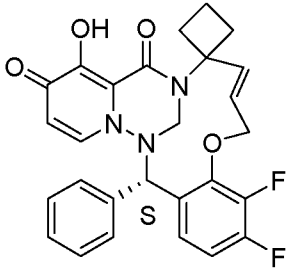
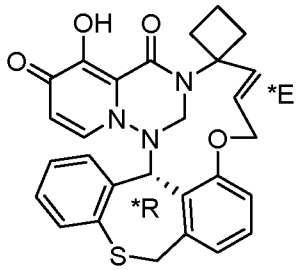
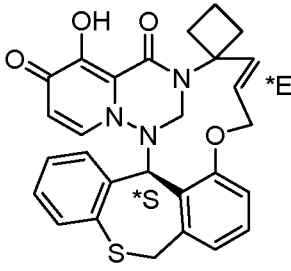
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
138AA 	0.0008	>0.05	0.004
138BB 	>0.1	>0.2	0.298
138C 	>0.1	>0.2	1.383
138D 	0.0009	>0.2	0.003
139AA 	8.321	26.9	5.093

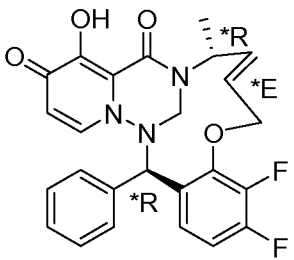
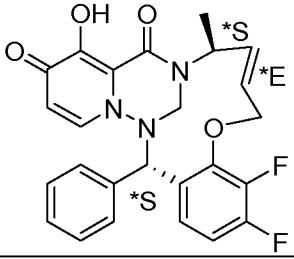
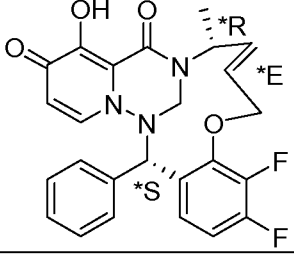
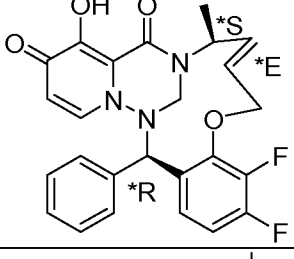
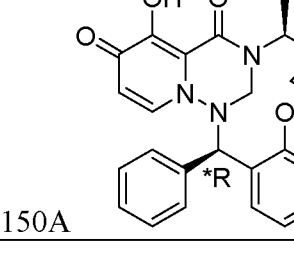
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
139BB 	>0.025	>0.05	0.0071
139AB 	4.892	35.9	3.025
139BA 	0.0446	>0.1	0.013
140A 	0.0963	9.96	0.606
140B 	0.0003	>0.05	0.003

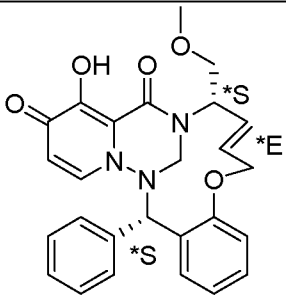
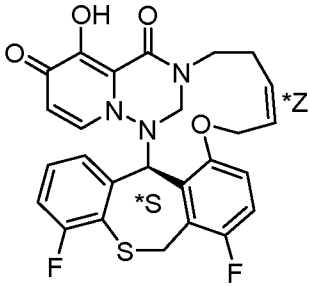
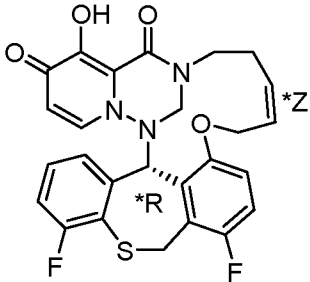
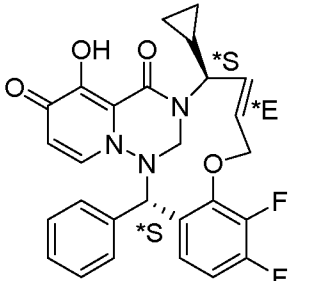
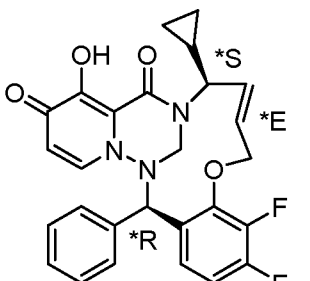
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
141AA 	0.0015	>0.05	0.009
141BB 	0.6266	>20	0.634
141AB 	0.0020	>0.05	0.006
141BA 	0.3059	>20	0.444
140C 	0.0374	>10	0.165

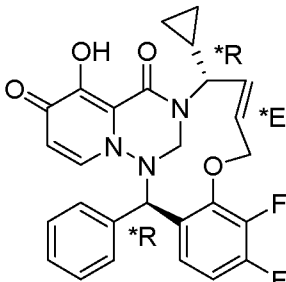
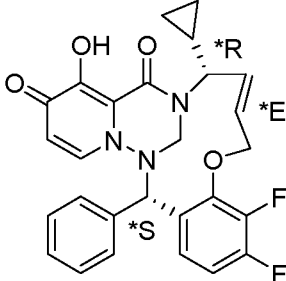
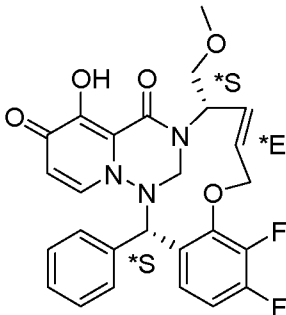
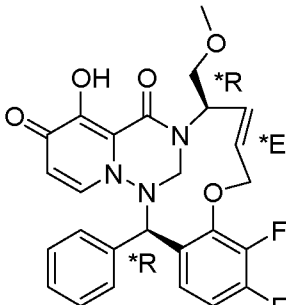
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
140D 	0.0012	>0.05	0.001
138AB 	0.0015	>0.05	0.008
138BA 	ND	ND	3.887
142 	prodrug		
143 	prodrug		

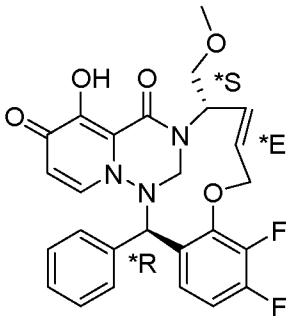
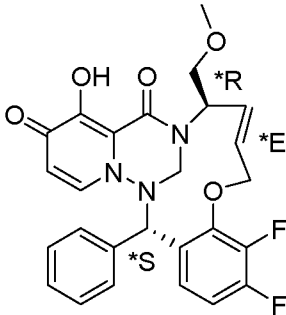
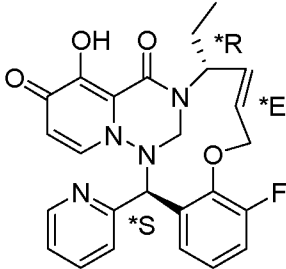
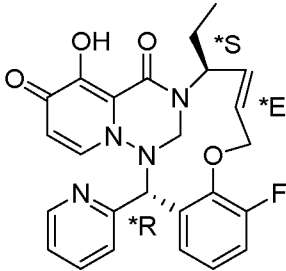
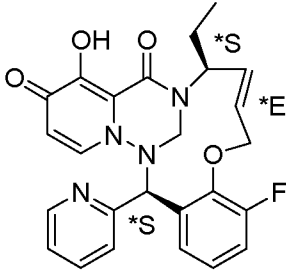
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
144AA 	>0.1	>0.2	
144AB 	>0.1	>0.2	
144BB 	0.0513	>4	
144BA 	0.0729	>0.2	
145A 	0.0031	>0.1	0.0067

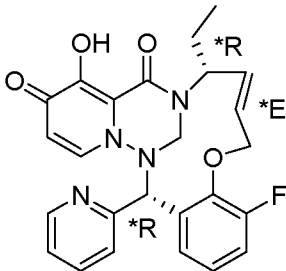
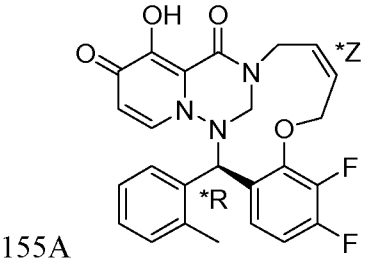
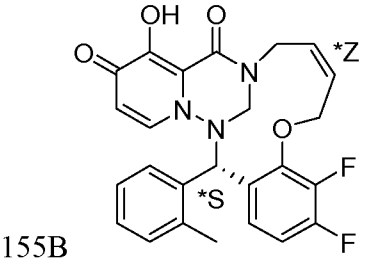
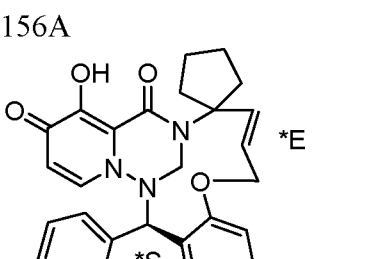
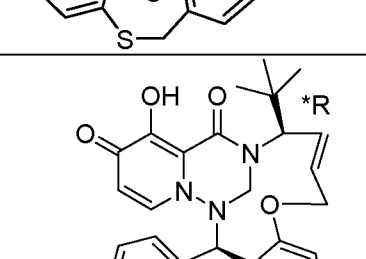
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
145B 	0.31	>10	>100
146A 	0.00065	>0.1	0.0063
146B 	0.34	>10	>100
147A 	>5	>10	>100
147B 	0.00033	>0.1	0.010

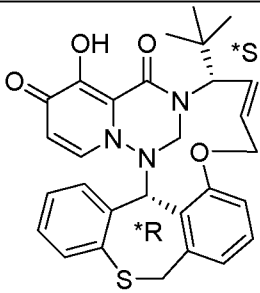
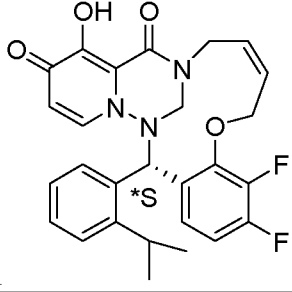
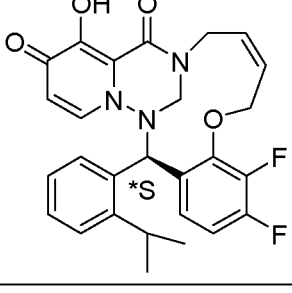
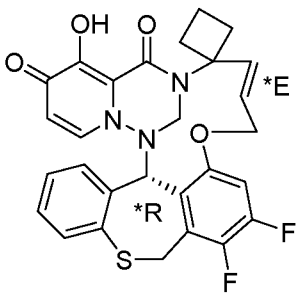
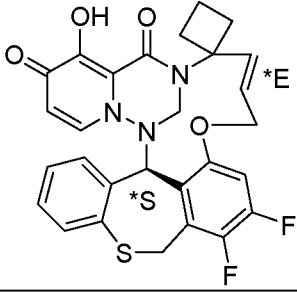
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
148AA 	0.0016	>0.05	0.0046
148BB 	>5	>10	0.47
148BA 	2.6	>10	>100
148BB 	0.0014	>0.1	0.0062
150A 	0.009	>0.1	0.033

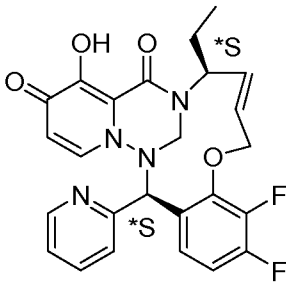
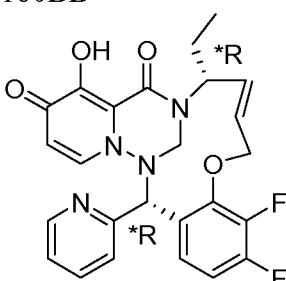
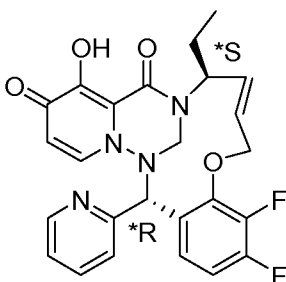
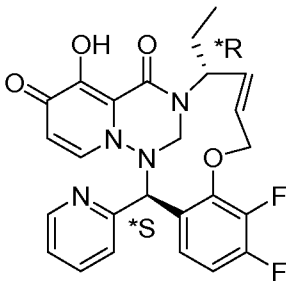
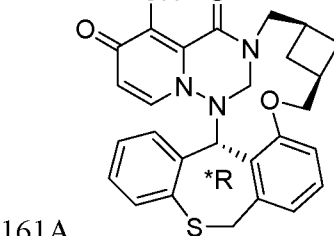
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
150B 	3.26	>10	12.76
151B 	0.0044	>0.1	0.0081
151A 	>0.05	>0.1	0.052
152AA 	>0.05	>0.1	11.04
152BA 	0.0013	>0.2	0.0012

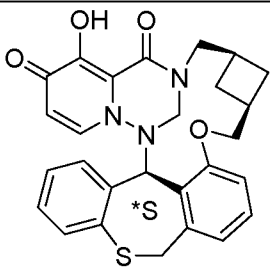
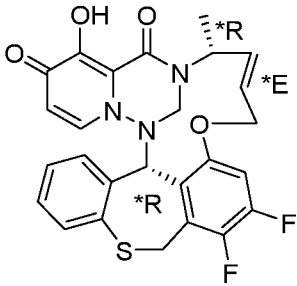
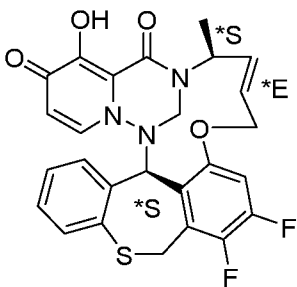
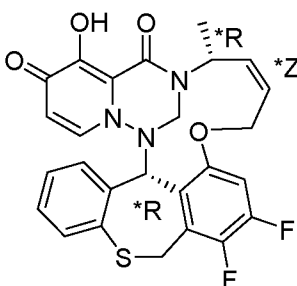
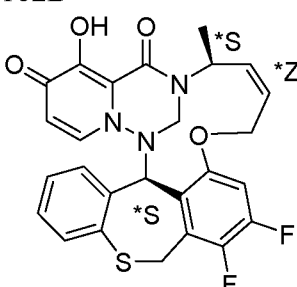
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
152BB 	0.0018	>0.2	0.0048
152AB 	>0.05	>0.1	21.69
153AA 	>0.05	>0.1	0.4
153BB 	0.0026	>0.1	0.004

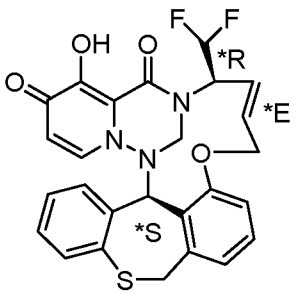
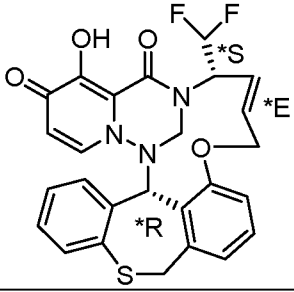
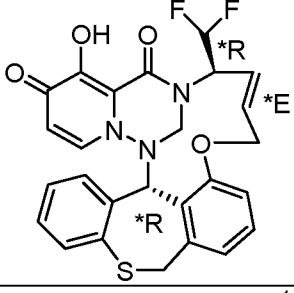
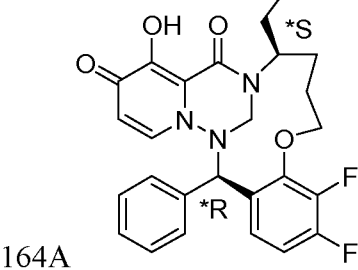
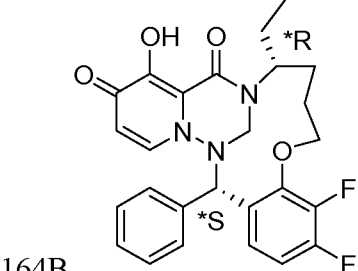
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
153BA 	0.0042	>0.1	0.0091
153AB 	>0.05	>0.1	0.52
154AA 	>0.05	>0.1	2.98
154BB 	0.0034	>0.1	0.0042
154AB 	>0.05	>0.1	5.15

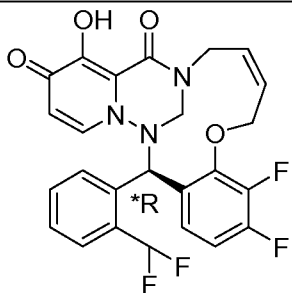
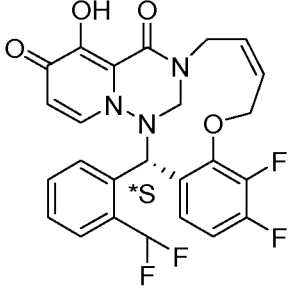
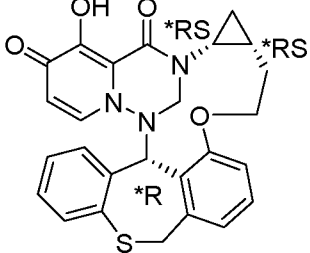
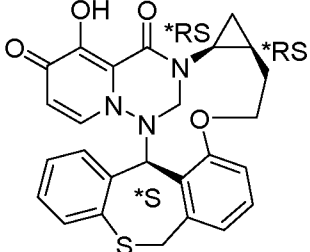
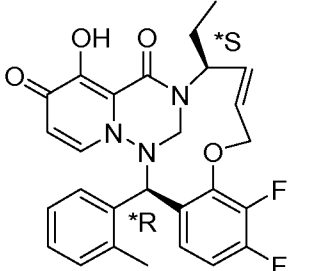
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
154BA 	0.0068	>0.1	0.011
155A 	0.0012	>0.1	0.0028
155B 	>0.05	>0.1	0.61
156A 	0.00051	>0.1	0.013
157A 	0.0013	>0.1	0.029

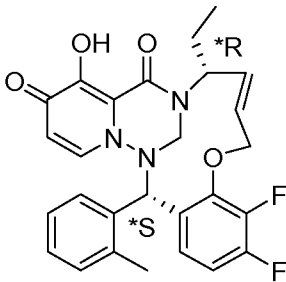
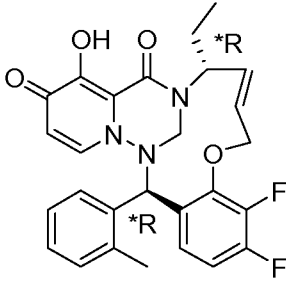
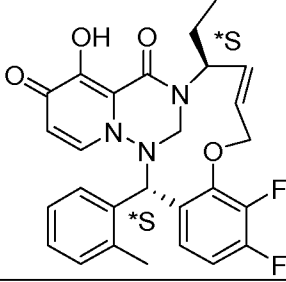
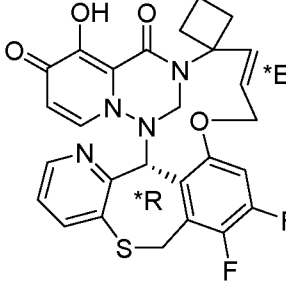
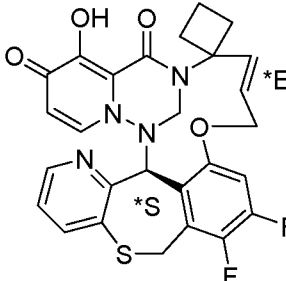
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
 157B	>0.05	>0.1	13.54
 158A	>0.05	>0.1	>100
 158B	>0.05	>0.1	0.38
 159A	>0.05	>0.1	>100
 159B	0.00019	>0.1	0.03

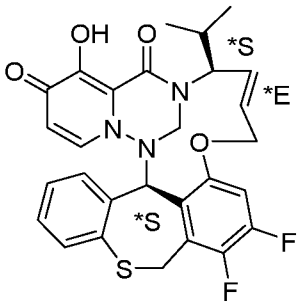
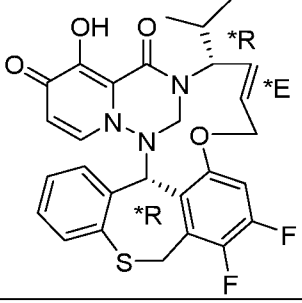
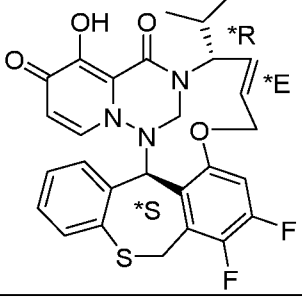
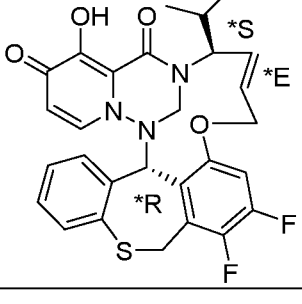
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
160AA 	0.0052	>0.1	0.011
160BB 	>0.05	>0.1	51.97
160BA 	>0.05	>0.1	>100
160AB 	0.0028	>0.1	0.0084
161A 	>0.05	>0.1	Nd

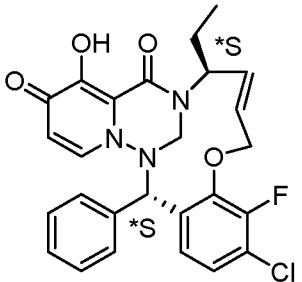
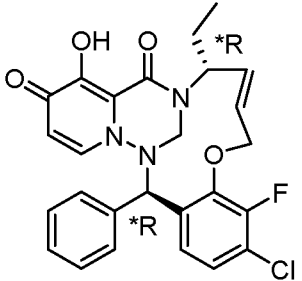
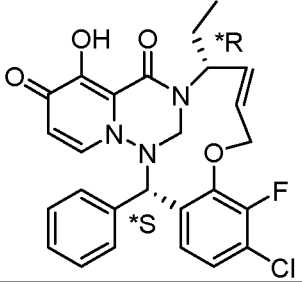
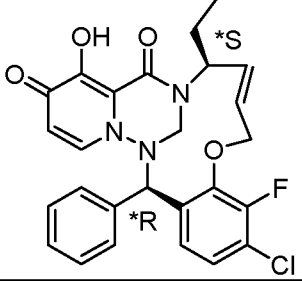
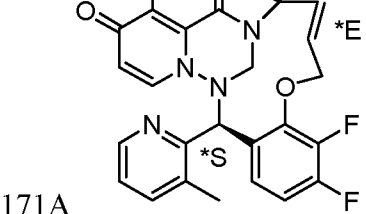
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
161B 	0.015	>0.1	0.041
162A 	>0.05	>0.1	0.57
162B 	0.00023	>0.1	0.0043
162C 	0.01	>0.1	0.051
162D 	0.00051	>0.1	0.002

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
163AA 	0.0019	>0.1	0.026
163BB 	>0.05	>0.1	69.43
163BA 	>0.05	>0.1	>100
164A 	>0.05	>0.1	10.85
164B 	0.0024	>0.1	0.018

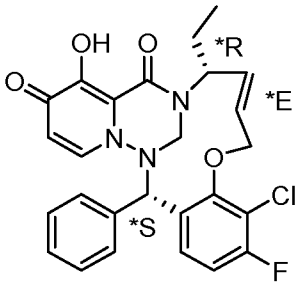
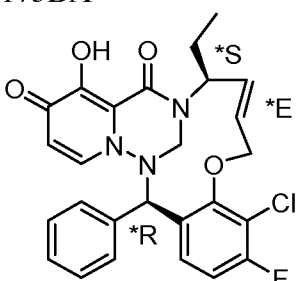
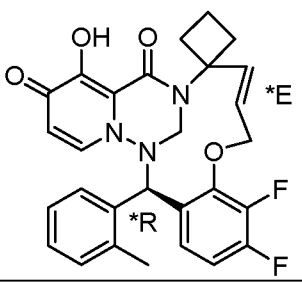
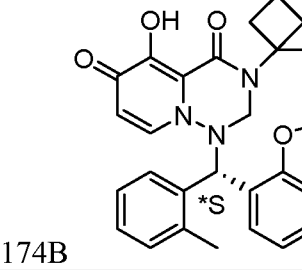
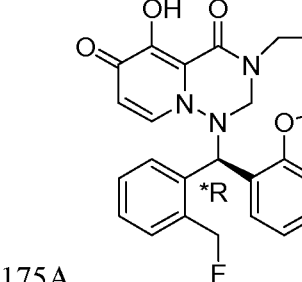
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
 165A	0.0072	>0.1	0.003
 165B	>0.05	>0.1	nd
 166A	>0.05	>0.1	0.66
 166B	0.028	nd	0.011
 167AA	0.00091	nd	0.0053

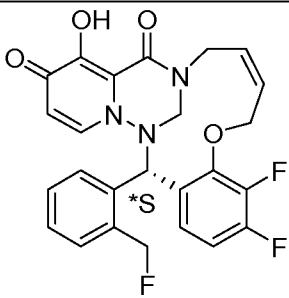
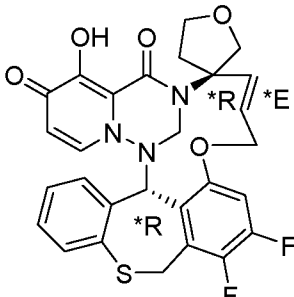
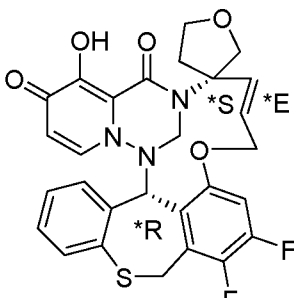
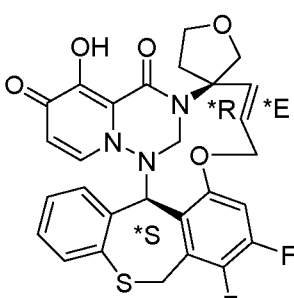
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167BB 	>0.05	nd	2.02
167AB 	0.00096	nd	0.006
167BA 	>0.05	nd	0.57
168A 	>0.05	>0.1	21.35
168B 	0.0006	nd	0.0052

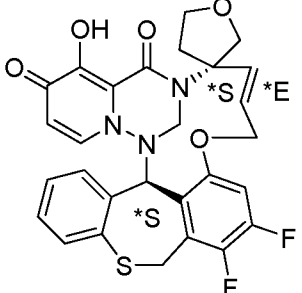
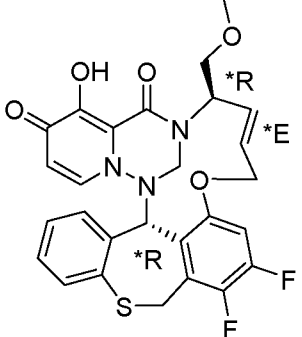
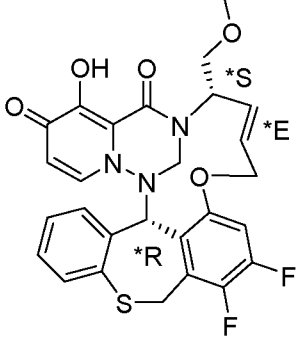
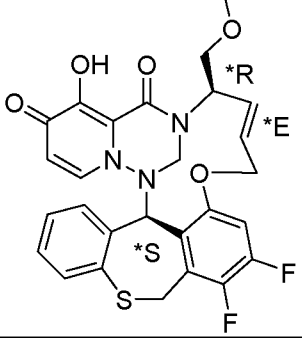
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
169AA 	0.048	>0.1	1.76
169BB 	0.0013	>0.1	0.0054
169AB 	>0.05	>0.1	4.64
169BA 	0.00083	nd	0.0093

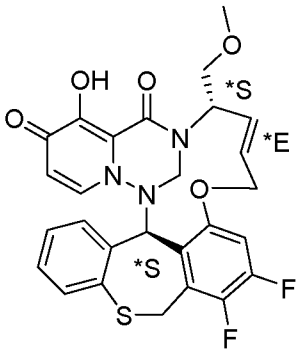
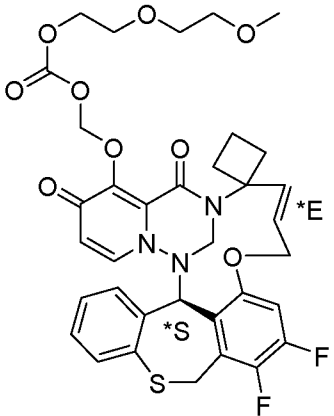
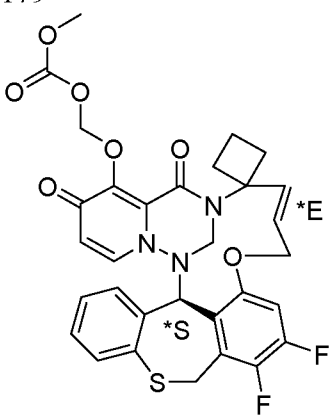
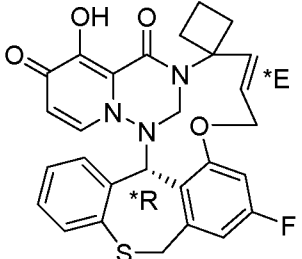
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
170AA 	>0.05	>0.1	2.88
170BB 	0.002	nd	0.0066
170AB 	>0.05	>0.1	1.34
170BA 	0.024	nd	0.0081
171A 	0.0013	>0.1	0.0083

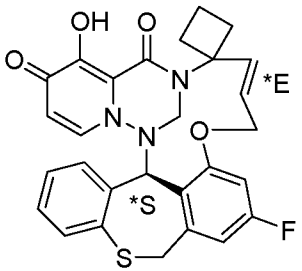
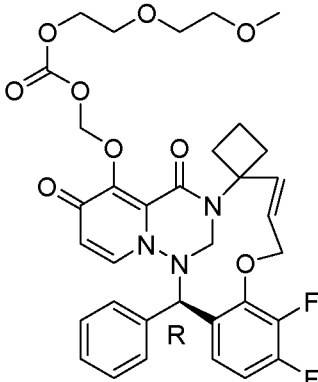
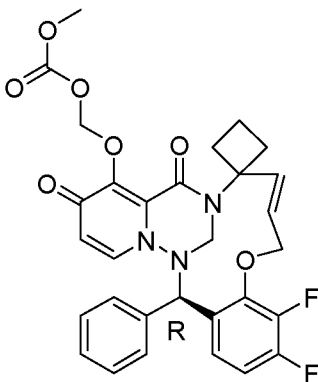
Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM
171B 	nd	nd	11.27
172A 	0.0029	>0.1	0.0077
172B 	>0.05	>0.1	29.25
173AA 	nd	nd	3.4
173BB 	nd	nd	0.011

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
173AB 	nd	nd	4.15
173BA 	0.026	nd	0.0067
174A 	nd	nd	0.25
174B 	0.0012	nd	0.0038
175A 	0.0023	nd	0.0019

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
 175B	nd	nd	0.29
 176AA	nd	nd	5.96
 176AB	nd	nd	nd
 176BA	0.0011	nd	0.0065

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
176BB 	0.0014	nd	0.0051
177AA 	0.015	nd	0.41
177AB 	0.00067	nd	0.0052
177BA 	nd	nd	nd

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
177BB 	nd	nd	nd
178 	prodrug		
179 	Prodrug		
180A 	0.029	nd	nd

Compound number	A549_A(H1N1) EC ₅₀ (uM)	CC ₅₀ (μM)	FRET_ _IC ₅₀ (uM)
180B 	0.00036	nd	nd
181 	Prodrug		
182 	Prodrug		

List of abbreviations:

EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

5 HOBt: 1-hydroxybenzotriazole

Rt: room temperature

DMF: dimethylformamide

DCE: dichloroethane

DMT: 2,4,6-trimercaptotriazine

10 TFA: trifluoro acetic acid

TFFA: trifluoroacetic anhydride

Rpm: rotations per minute

HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium
3-oxide hexafluorophosphate

SFC: supercritical fluid chromatography

5 DBAD: di-tert-butyl azodicarboxylate

o/n: overnight

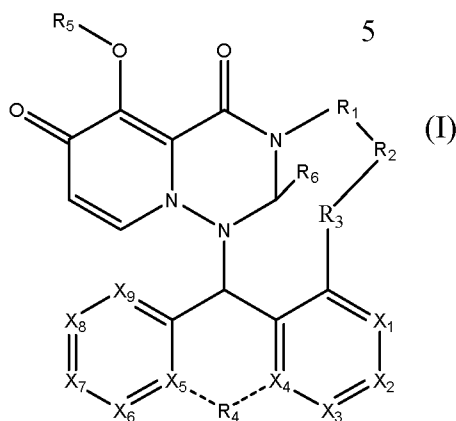
MTBE: methyl tert-butyl ether

ACCN: 1,1'-azobis(cyclohexanecarbonitrile)

10 PPA: polyphosphoric Acid

Claims

1. A compound having Formula (I)



- and all possible stereoisomeric forms thereof, wherein:
- R_1 is C, $-\text{CH}_2\text{-CH}_2\text{-O-}$, C_{3-6} cycloalkyl, oxetanyl, C_{1-3} alkyl-cyclopropyl or C_{1-3} alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo, oxo, CH_2 -methoxy, C_{1-4} alkyl, C_{1-6} cycloalkyl and tetrahydrofuran;
- R_2 is C_{1-6} alkyl, C_{1-6} alkyl-O-, C_{1-6} alkyl-N-, C_{2-6} alkenyl, C_{2-6} alkenyl-O- or C_{2-6} alkenyl-N- optionally substituted by one or more substituents independently selected from halo, oxo or C_{1-4} alkyl;
- R_3 is C or O optionally substituted by one or more substituents independently selected from halo, oxo and methyl;
- or, R_2 and R_3 together form C_{2-8} alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;
- X_1 to X_9 are each N or C and wherein any of X_1 to X_9 is C, said C is optionally substituted by one or more substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, CHF_2 , CH_2F , CF_3 , OCF_3 , SCF_3 , OCH_3 , SCH_3 , $\text{S-(O)}_2\text{-CH}_3$ or halogen;
- the dotted lines are each an optional bond;
- R_4 is absent, $-\text{CH}_2\text{-CH}_2-$, $-\text{O-CH}_2-$, $-\text{S-CH}_2-$, $\text{S-(O)}_2\text{-CH}_2$ or cyclopropyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;
- R_5 is H, $-\text{C(=O)Y}$, $-(\text{CH}_2)\text{-O-(C=O)-Y}$, $-(\text{CH}_2)\text{-O-(C=O)-O-Y}$, $-(\text{CHCH}_3)\text{-O-(C=O)-Y}$, $-(\text{CHCH}_3)\text{-O-(C=O)-O-Y}$, $-(\text{CH}_2)\text{-O-(C=O)-NH-Y}$, $-(\text{CH}_2)\text{-O-(C=O)C(R}_7\text{)-NH-(R}_8\text{)}$;

Y is C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, C₁₋₄alkyl-(O-R₇), C₁₋₄alkyl-N-(R₇)(R₈), R₇-O-R₈-O-CH₂;

and R₇ and R₈ are independently hydrogen or C₁₋₄alkyl;

R₆ is H, methyl or CH₂-O-CH₃;

5 and the pharmaceutically acceptable salts, polymorphs and solvates thereof.

2. The compound according to claim 1 wherein

R₁ is C, -CH₂-CH₂-O-, C₃₋₆cycloalkyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo, oxo, CH₂-methoxy, C₁₋₄alkyl and C₁₋₆ cycloalkyl;

R₂ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkenyl-O- or C₂₋₆alkenyl-N- optionally substituted by one or more substituents independently selected from halo, oxo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

or, R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

the dotted lines are each an optional bond;

R₄ is absent, -CH₂-CH₂-, -O-CH₂- or -S-CH₂- optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

R₅ is H, -C(=O)Y, -(CH₂)-O-(C=O)-Y, -(CH₂)-O-(C=O)-O-Y, -(CHCH₃)-O-(C=O)-Y, -(CHCH₃)-O-(C=O)-O-Y, -(CH₂)-O-(C=O)-NH-Y, -(CH₂)-O-(C=O)C(R₇)-NH-(R₈);

Y is C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, C₁₋₄alkyl-(O-R₇), C₁₋₄alkyl-N-(R₇)(R₈), R₇-O-R₈-O-CH₂;

and R₇ and R₈ are independently hydrogen or C₁₋₄alkyl;

R₆ is H or methyl.

3. The compound according to any of claims 1 or 2 wherein

R₁ is C, C₃₋₆cycloalkyl, C₁₋₃alkyl-cyclopropyl or C₁₋₃alkyl-cyclobutyl, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

R₂ is C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo and methyl;

or, R₂ and R₃ together form C₂₋₈alkenyl optionally substituted by one or more substituents independently selected from halo, oxo and methyl;

5 X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

the dotted lines are each an optional bond;

10 R₄ is absent or -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ is H; and

R₆ is H or methyl.

15 4. The compound according to any of claims 1-3 wherein

R₁ is C, C₃₋₆cycloalkyl or C₁₋₃alkyl-cyclopropyl, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

R₂ is C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

20 R₃ is C or O optionally substituted by one or more substituents independently selected from halo and methyl;

X₁ to X₉ are each N or C and wherein any of X₁ to X₉ is C, said C is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, CHF₂, CH₂F, CF₃, OCF₃, SCF₃, OCH₃, SCH₃, S-(O)₂-CH₃ or halogen;

25 the dotted lines are each an optional bond;

R₄ is absent or -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ is H; and

30 R₆ is H or methyl.

5. The compound according to any of claims 1-4 wherein

R₁ is C, C₃₋₆cycloalkyl or C₁₋₃alkyl-cyclopropyl, optionally substituted by one or more substituents independently selected from, halo and C₁₋₄alkyl;

35 R₂ is C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted by one or more substituents independently selected from halo or C₁₋₄alkyl;

R₃ is C or O optionally substituted by one or more substituents independently selected from halo and methyl;

X₁ to X₉ are each C which is optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, C₃₋₆cycloalkyl or halogen;

the dotted lines are each an optional bond;

R₄ is absent or -S-CH₂- optionally substituted by one or more substituents independently selected from halo and methyl;

R₅ is H; and

R₆ is H.

6. A pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any of claims 1-5 and one or more pharmaceutically acceptable excipients, diluents or carriers.

7. A compound of Formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any of claims 1-5, or a pharmaceutical composition according to claim 3 for use as a medicament.

8. A compound of Formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any of claims 1-5, or a pharmaceutical composition according to claim 4, for use in the prevention or treatment of influenza viral infections.

9. A compound of Formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any of claims 1-5, or a pharmaceutical composition according to claim 4, for use in the prevention or treatment of influenza A viral infection, influenza B viral infections or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/058591

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/14 A61P31/16 A61K31/5395 A61K31/53
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)

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 practicable, search terms used)

EPO-Internal, CHEM ABS Data, 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	EP 2 444 400 A1 (SHIONOGI & CO [JP]) 25 April 2012 (2012-04-25) claims 1,32-35 -----	1-9
A	EP 2 620 436 A1 (SHIONOGI & CO [JP]) 31 July 2013 (2013-07-31) claims 1,22-24 -----	1-9
A	US 2018/057501 A1 (JAIN RAMA [US] ET AL) 1 March 2018 (2018-03-01) claims 1,22 -----	1-9
A	WO 2015/038660 A1 (ALIOS BIOPHARMA INC [US]) 19 March 2015 (2015-03-19) claims 1,4,92,95 -----	1-9

☐ 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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

12 November 2019

Date of mailing of the international search report

25/11/2019

Name and mailing address of the ISA/

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Authorized officer

Schuemacher, Anne

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2019/058591

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