

C-3 CYCLOALKENYL TRITERPENOID WITH HIV MATURATION
INHIBITORY ACTIVITY

CROSS REFERENCE TO RELATED APPLICATION

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This non-provisional application claims the benefit of U.S. non-provisional application serial number 13/760,726 filed February 6, 2013 and U.S. provisional application serial number 61/599,040 filed February 15, 2012.

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FIELD OF THE INVENTION

The present invention relates to novel compounds useful against HIV and, more particularly, to compounds derived from betulinic acid and other structurally-related compounds which are useful as HIV maturation inhibitors, and to pharmaceutical compositions containing same, as well as to methods for their preparation.

BACKGROUND OF THE INVENTION

HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 45-50 million people infected worldwide at the end of 2010. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations: zidovudine (or AZT or Retrovir[®]), didanosine (or Videx[®]), stavudine (or Zerit[®]), lamivudine (or 3TC or EpiVir[®]), zalcitabine (or DDC or Hivid[®]), abacavir succinate (or Ziagen[®]), Tenofovir disoproxil fumarate salt (or Viread[®]), emtricitabine (or FTC - Emtriva[®]), Combivir[®] (contains -3TC plus AZT), Trizivir[®] (contains abacavir, lamivudine, and zidovudine), Epzicom[®] (contains abacavir and lamivudine), Truvada[®] (contains Viread[®] and Emtriva[®]); non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune[®]), delavirdine (or Rescriptor[®]) and efavirenz (or Sustiva[®]), Atripla[®] (Truvada[®] + Sustiva[®]), and etravirine, and peptidomimetic protease inhibitors

or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra[®] (lopinavir and Ritonavir), darunavir, atazanavir (Reyataz[®]) and tipranavir (Aptivus[®]) and cobicistat, and integrase inhibitors such as raltegravir (Isentress[®]), and entry inhibitors such as enfuvirtide (T-20) (Fuzeon[®]) and maraviroc (Selzentry[®]).

Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients may ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents further being studied by a number of investigators.

HIV attachment inhibitors are a further subclass of antiviral compounds that bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents. In particular, US 7,354,924 and US 7,745,625 are illustrative of HIV attachment inhibitors.

Another emerging class of compounds for the treatment of HIV are called HIV maturation inhibitors. Maturation is the last of as many as 10 or more steps in HIV replication or the HIV life cycle, in which HIV becomes infectious as a consequence of several HIV protease-mediated cleavage events in the gag protein that ultimately results in release of the capsid (CA) protein. Maturation inhibitors prevent the HIV capsid from properly assembling and maturing, from forming a protective outer coat, or from emerging from human cells. Instead, non-infectious viruses are produced, preventing subsequent cycles of HIV infection.

Certain derivatives of betulinic acid have now been shown to exhibit potent anti-HIV activity as HIV maturation inhibitors. For example, US 7,365,221 discloses monoacylated betulin and dihydrobetuline derivatives, and their use as anti-HIV agents. As discussed in the '221 reference, esterification of betulinic acid (1) with certain substituted acyl groups, such as 3',3'-dimethylglutaryl and 3',3'-dimethylsuccinyl groups produced derivatives having enhanced activity (Kashiwada, Y., et al., J. Med. Chem. 39:1016-1017 (1996)). Acylated betulinic acid and dihydrobetulinic acid derivatives that are potent anti-HIV agents are also described in U.S. Pat. No. 5,679,828. Esterification of the hydroxyl in the 3 carbon of betulin with succinic acid also produced a compound capable of inhibiting HIV-1 activity (Pokrovskii, A. G., et al., Gos. Nauchnyi Tsentr Virusol. Biotekhnol. "Vector", Koltsovo, Russia. Khimiya v Interesakh Ustoichivogo Razvitiya, 9:485-491 (2001)).

Other references to the use of treating HIV infection with compounds derived from betulinic acid include US 2005/0239748 and US 2008/0207573, as well as WO2006/053255, WO2009/100532 and WO2011/007230.

One HIV maturation compound that has been in development has been identified as Bevirimat or PA-457, with the chemical formula of $C_{36}H_{56}O_6$ and the IUPAC name of 3 β -(3-carboxy-3-methyl-butanoyloxy) lup-20(29)-en-28-oic acid.

Reference is also made herein to the applications by Bristol-Myers Squibb entitled "MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,706 filed on June 2, 2011 (US 2012-0142707) and "C-28

AMIDES OF MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,722, filed on June 2, 2011 (US 2012-0142653). Reference is also made to the application entitled "C-28 AMINES OF C-3 MODIFIED BETULINIC ACID DERIVATIVES AS HIV MATURATION

5 INHIBITORS" USSN 13/359,680, filed on January 27, 2012. In addition, reference is made to the application entitled "C-17 AND C-3 MODIFIED TRITERPENOID WITH HIV MATURATION INHIBITORY ACTIVITY" USSN 13/359,727 filed on January 27, 2012.

10 What is now needed in the art are new compounds which are useful as HIV maturation inhibitors, as well as new pharmaceutical compositions containing these compounds.

SUMMARY OF THE INVENTION

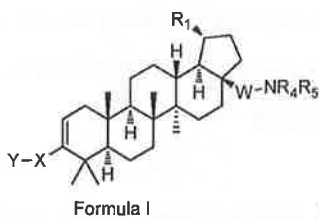
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The present invention provides compounds of Formulas I, II, III and IV below, including pharmaceutically acceptable salts thereof, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formulas I – IV are effective antiviral agents, particularly as inhibitors of

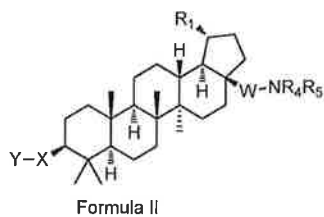
20 HIV. They are useful for the treatment of HIV and AIDS.

One embodiment of the present invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

25 a compound of formula I

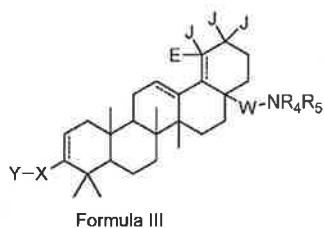


a compound of formula II



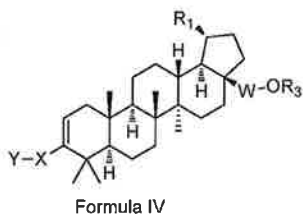
a compound of formula III

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; and

a compound of formula IV



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wherein R₁ is isopropenyl or isopropyl;

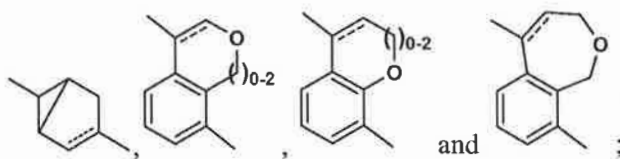
J and E are independently -H or -CH₃, and E is absent when the double bond is present;

15

X is selected from the group of C₄₋₈ cycloalkyl, C₄₋₈ cycloalkenyl, C₄₋₉ spirocycloalkyl, C₄₋₉ spirocycloalkenyl, C₄₋₈ oxacycloalkyl, C₄₋₈ dioxacycloalkyl, C₆₋₈ oxacycloalkenyl, C₆₋₈ dioxacycloalkenyl, C₆ cyclodialkenyl, C₆ oxacyclodialkenyl, C₆₋₉ oxaspirocycloalkyl and C₆₋₉ oxaspirocycloalkenyl ring, wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C₁₋₆ alkyl, -C₁₋₆ alkoxy, -C₁₋₆ alkyl-Q, -alkylsubstituted C₁₋₆ alkyl-Q, -CN, -CF₂Q, -NR₈R₉, -COOR₂ and -CONR₂R₂;

20

X can also be selected from the group of:



- 5 wherein Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, $-OR_2$, $-COOR_3$, $-NR_2R_2$, $-SO_2R_7$, $-CONHSO_2R_3$, and $-CONHSO_2NR_2R_2$;

R_2 is $-H$, $-C_{1-6}$ alkyl, $-alkylsubstituted\ C_{1-6}\ alkyl$ or $-arylsubstituted\ C_{1-6}\ alkyl$;

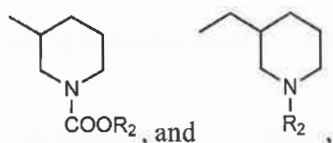
- 10 Y is selected from the group of $-COOR_2$, $-C(O)NR_2SO_2R_3$, $-C(O)NHSO_2NR_2R_2$, $-NR_2SO_2R_2$, $-SO_2NR_2R_2$, $-C_{3-6}$ cycloalkyl- $COOR_2$, $-C_{2-6}$ alkenyl- $COOR_2$, $-C_{2-6}$ alkynyl- $COOR_2$, $-C_{1-6}$ alkyl- $COOR_2$, $-alkylsubstituted\ C_{1-6}\ alkyl$, $-COOR_2$, CF_2-COOR_2 , $-NHC(O)(CH_2)_n-COOR_2$, $-SO_2NR_2C(O)R_2$, tetrazole, and $-CONHOH$, wherein $n=1-6$;

15

W is absent, CH_2 or CO ;

R_3 is $-C_{1-6}$ alkyl or $-alkylsubstituted\ C_{1-6}\ alkyl$;

- 20 R_4 is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $C(OR_3)_2-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl, $-C_{1-6}$ alkyl- Q_1 , $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl- Q_1 , aryl, heteroaryl, substituted heteroaryl, $-COR_6$, $-COCOR_6$, $-SO_2R_7$, $-SO_2NR_2R_2$,



- 25 with the proviso that R_4 or R_5 cannot be COR_6 or $COCOR_6$ when W is CO ;

wherein Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, $-CF_3$, $-OR_2$, $-COOR_2$, $-NR_8R_9$, $-CONR_{10}R_{11}$ and $-SO_2R_7$;

R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₁₀, -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

- 5 with the proviso that only one of R₄ or R₅ can be selected from the group of -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;
or when W is absent or is CH₂, then R₄ and R₅ can be taken together with the adjacent N to form



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R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

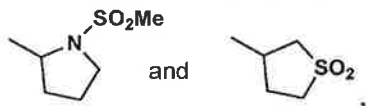
- 15 wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

R₇ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -CF₃, aryl, and heteroaryl;

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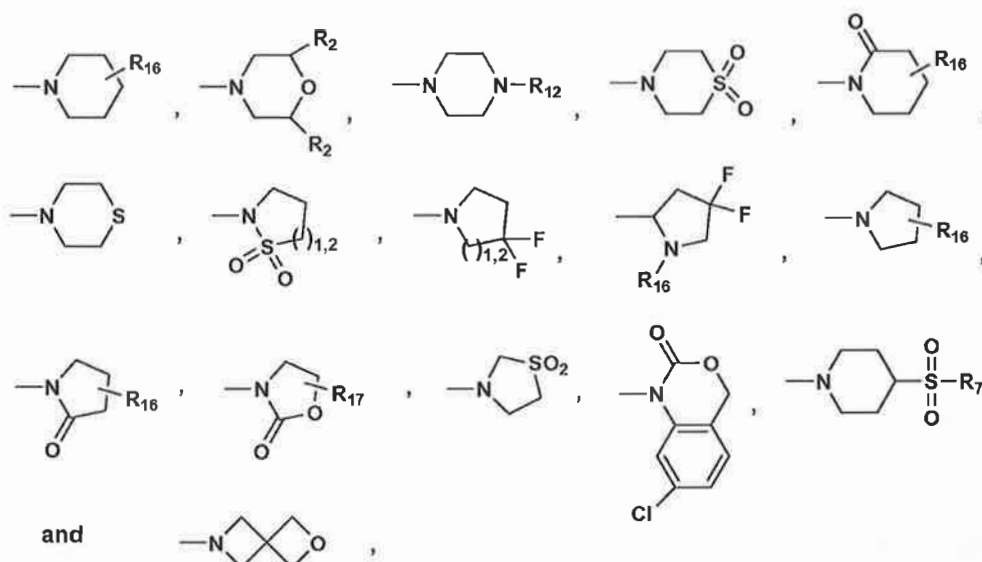
R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,

and R₈ and R₉ can also be independently selected from the group of



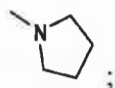
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or R₈ and R₉ are taken together with the adjacent N to form a cycle selected from the group of:



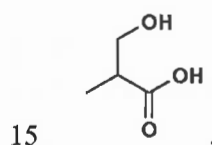
with the proviso that only one of R_8 or R_9 can be $-\text{COOR}_3$;

- R_{10} and R_{11} are independently selected from the group of -H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ substituted alkyl and $-\text{C}_{3-6}$ cycloalkyl,
- 5 or R_{10} and R_{11} are taken together with the adjacent N to form a cycle such as

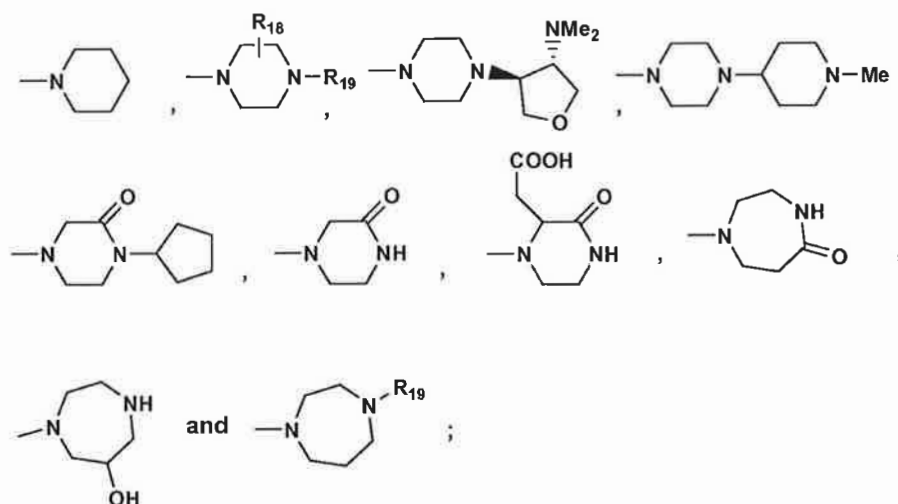


- R_{12} is selected from the group of $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkyl-OH; $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ substituted alkyl, $-\text{C}_{3-6}$ cycloalkyl, $-\text{COR}_7$, $-\text{COONR}_{22}\text{R}_{23}$, $-\text{SOR}_7$, and $-\text{SONR}_{24}\text{R}_{25}$;
- 10

R_{13} and R_{14} are independently selected from the group of -H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{3-6}$ cycloalkyl, $-\text{C}_{1-6}$ substituted alkyl, $-\text{C}_{1-6}$ alkyl- Q_3 , $-\text{C}_{1-6}$ alkyl- C_{3-6} cycloalkyl- Q_3 , C_{1-6} substituted alkyl- Q_3 and



or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:



Q_3 is selected from the group of heteroaryl, substituted heteroaryl, $-NR_{20}R_{21}$, $CONR_2R_2$, $-COOR_2$, $-OR_2$, and $-SO_2R_3$;

5

R_{15} is selected from the group of $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl- Q_3 , $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl- Q_3 and $-C_{1-6}$ substituted alkyl- Q_3 ;

R_{16} is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-NR_2R_2$, and $-COOR_3$;

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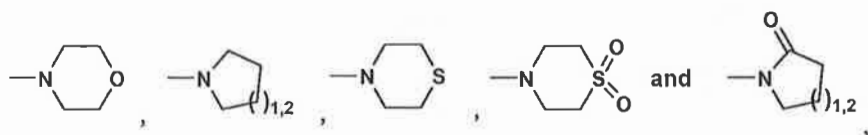
R_{17} is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-COOR_3$, and aryl;

R_{18} is selected from the group of $-COOR_2$ and $-C_{1-6}$ alkyl- $COOR_2$;

15 R_{19} is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- Q_4 , $-COR_3$, $-COOR_3$, wherein Q_4 is selected from the group of $-NR_2R_2$ and $-OR_2$;

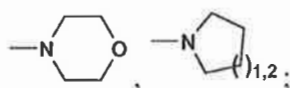
R_{20} and R_{21} are independently selected from the group of $-H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ substituted alkyl- OR_2 , and $-COR_3$,

20 or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be $-\text{COR}_3$;

- 5 R_{22} and R_{23} are independently selected from the group of H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ substituted alkyl, and $-\text{C}_{1-6}$ cycloalkyl,
or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



- 10 R_{24} and R_{25} are independently from the group of H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ substituted alkyl, $-\text{C}_{1-6}$ alkyl- Q_5 , $-\text{C}_{1-6}$ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and Q_5 is selected from the group of halogen and SO_2R_3 .

- In a further embodiment, there is provided a method for treating mammals
15 infected with a virus, especially wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound which is selected from the group of compounds of Formulas I, II, III and IV above, and one or more pharmaceutically acceptable carriers, excipients or diluents. Optionally, the compound of Formulas I, II, III, and/or IV can be administered in combination with an antiviral
20 effective amount of another- AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

- Another embodiment of the present invention is a pharmaceutical composition
25 comprising an antiviral effective amount of a compound which is selected from the group of compounds of Formulas I, II, III, and IV, and one or more pharmaceutically acceptable carriers, excipients, and diluents; and optionally in combination with an antiviral effective amount of another AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an
30 immunomodulator; and (d) other HIV entry inhibitors.

In another embodiment of the invention there is provided one or more methods for making the compounds of Formulas I, II, III and IV herein.

Also provided herein are intermediate compounds useful in making the
5 compounds of Formulas I, II, III and IV herein.

The present invention is directed to these, as well as other important ends, hereinafter described.

10 DETAILED DESCRIPTION OF THE EMBODIMENTS

Since the compounds of the present invention may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present disclosure includes the individual diastereoisomeric and enantiomeric forms of the compounds of
15 Formulas I, II and III in addition to the mixtures thereof.

Definitions

Unless otherwise specifically set forth elsewhere in the application, one or more
20 of the following terms may be used herein, and shall have the following meanings:

“H” refers to hydrogen, including its isotopes, such as deuterium.

The term “C₁₋₆ alkyl” as used herein and in the claims (unless specified otherwise)
25 mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

“C₁–C₄ fluoroalkyl” refers to F-substituted C₁–C₄ alkyl wherein at least one H atom is substituted with F atom, and each H atom can be independently substituted by F
30 atom;

“Halogen” refers to chlorine, bromine, iodine or fluorine.

An "aryl" or "Ar" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and $-NR^xR^y$, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranal, tetrahydropyranal, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl, diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encompass systems which would not exist.

- 5 The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidiny, piperidyl, piperaziny, imidazoliny, thiazolidiny, 3-pyrrolidin-1-yl, morpholiny, thiomorpholiny and tetrahydropyrany. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, 10 heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, 15 guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined above.

- An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms 20 (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent 25 group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, 30 trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, amidino, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an $-OH$ group.

An "alkoxy" group refers to both an $-O$ -alkyl and an $-O$ -cycloalkyl group as defined herein.

An "aryloxy" group refers to both an $-O$ -aryl and an $-O$ -heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl- O - group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic- O - group with heteroalicyclic as defined herein.

A “thiohydroxy” group refers to an –SH group.

5 A “thioalkoxy” group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A “thioaryloxy” group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

10 A “thioheteroaryloxy” group refers to a heteroaryl-S- group with heteroaryl as defined herein.

A “thioheteroalicycloxy” group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

15

A “carbonyl” group refers to a –C(=O)-R” group, where R” is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

20

An “aldehyde” group refers to a carbonyl group where R” is hydrogen.

A “thiocarbonyl” group refers to a –C(=S)-R” group, with R” as defined herein.

25 A “Keto” group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroalicyclic group.

30 A “trihalomethanecarbonyl” group refers to a $Z_3CC(=O)-$ group with said Z being a halogen.

A “C-carboxy” group refers to a –C(=O)O-R” groups, with R” as defined herein.

An "O-carboxy" group refers to a $R''C(-O)O$ -group, with R'' as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R'' is hydrogen.

5 A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$ - groups with Z as defined above.

10

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$ - group with Z as defined above and R^x being H or (C_{1-6}) alkyl.

A "sulfinyl" group refers to a $-S(=O)-R''$ group, with R'' being (C_{1-6}) alkyl.

15

A "sulfonyl" group refers to a $-S(=O)_2R''$ group with R'' being (C_{1-6}) alkyl.

A "S-sulfonamido" group refers to a $-S(=O)_2NR^xR^y$, with R^x and R^y independently being H or (C_{1-6}) alkyl.

20

A "N-Sulfonamido" group refers to a $R''S(=O)_2NR_x$ - group, with R_x being H or (C_{1-6}) alkyl.

25 A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

30 A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$ - group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

An "amino" group refers to an $-NH_2$ group.

5

A "C-amido" group refers to a $-C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

10

A "N-amido" group refers to a $R^xC(=O)NR^y$ - group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group, with R^x , R^y , and R^{y2} independently being H or (C_{1-6}) alkyl.

15

A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x , R^y , and R^{y2} independently being H or (C_{1-6}) alkyl.

20

A "amidino" group refers to a $R^xR^yNC(=N)-$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "cyano" group refers to a $-CN$ group.

25

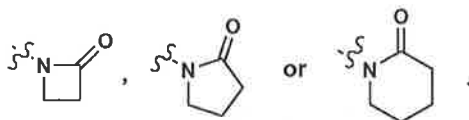
A "silyl" group refers to a $-Si(R'')_3$, with R'' being (C_{1-6}) alkyl or phenyl.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6}) alkyl.

A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group, with R^x , R^y , and R^{y2} independently being H or (C_{1-6}) alkyl.

30

A “4, 5, or 6 membered ring cyclic N-lactam” group refers to



A “spiro” group is a bicyclic organic group with rings connected through just one atom. The rings can be different in nature or identical. The connecting atom is also called the spiroatom, most often a quaternary carbon ("spiro carbon").

An “oxospiro” or “oxaspiro” group is a spiro group having an oxygen contained within the bicyclic ring structure. A “dioxospiro” or “dioxaspiro” group has two oxygens within the bicyclic ring structure.

Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

It is known in the art that nitrogen atoms in heteroaryl systems can be “participating in a heteroaryl ring double bond”, and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of the invention. The term “pharmaceutically acceptable salt” as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term “pharmaceutically acceptable salt” as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts,

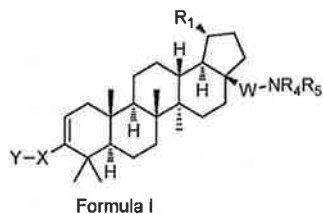
particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine,

5 triethanolamine or tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

As stated above, the compounds of the invention also include “prodrugs”. The term “prodrug” as used herein encompasses both the term “prodrug esters” and the term “prodrug ethers”.

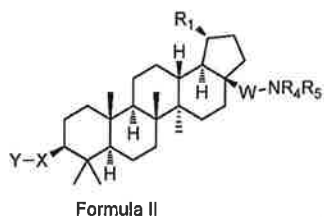
As set forth above, the invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

15 a compound of formula I

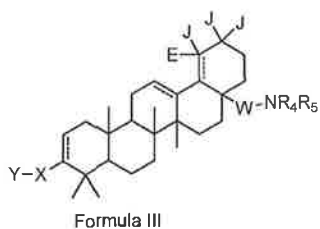


a compound of formula II

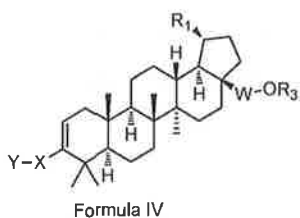
20



a compound of formula III



and a compound of formula IV

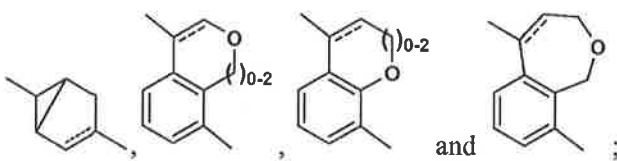


5

wherein R_1 is isopropenyl or isopropyl;

J and E are independently -H or -CH₃, and E is absent when the double bond is present;

- 10 X is selected from the group of C₄₋₈ cycloalkyl, C₄₋₈ cycloalkenyl, C₄₋₉ spirocycloalkyl, C₄₋₉ spirocycloalkenyl, C₄₋₈ oxacycloalkyl, C₄₋₈ dioxacycloalkyl, C₆₋₈ oxacycloalkenyl, C₆₋₈ dioxacycloalkenyl, C₆ cyclodialkenyl, C₆ oxacyclodialkenyl, C₆₋₉ oxaspirocycloalkyl and C₆₋₉ oxaspirocycloalkenyl ring, wherein X is substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C₁₋₆ alkyl, -C₁₋₆ alkoxy, -C₁₋₆ alkyl-Q, -alkylsubstituted C₁₋₆ alkyl-Q, -CN, -CF₂Q, -NR₈R₉, -COOR₂ and -CONR₂R₂;
- 15 X can also be selected from the group of:



- 20 wherein Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₃, -NR₂R₂, -SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

R_2 is -H, -C₁₋₆ alkyl, -alkylsubstituted C₁₋₆ alkyl or-arylsubstituted C₁₋₆ alkyl;

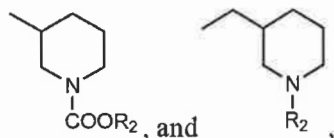
Y is selected from the group of -COOR₂, -C(O)NR₂SO₂R₃, -C(O)NHSO₂NR₂R₂,
 -NR₂SO₂R₂, -SO₂NR₂R₂, -C₃₋₆ cycloalkyl-COOR₂, -C₂₋₆ alkenyl-COOR₂, -C₂₋₆ alkynyl-
 5 COOR₂, -C₁₋₆ alkyl-COOR₂, -alkylsubstituted C₁₋₆ alkyl, -COOR₂, CF₂-COOR₂, -
 NHC(O)(CH₂)_n-COOR₂, -SO₂NR₂C(O)R₂, -tetrazole, and -CONHOH,
 wherein n=1-6;

W is absent, CH₂ or CO;

10

R_3 is -C₁₋₆ alkyl or -alkylsubstituted C₁₋₆ alkyl;

R_4 is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-C(OR₃)₂-C₃₋₆ cycloalkyl, -C₁₋₆
 substituted alkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-Q₁, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₁,
 15 aryl, heteroaryl, substituted heteroaryl, -COR₆, -COCOR₆, -SO₂R₇, -SO₂NR₂R₂,



with the proviso that R_4 or R_5 cannot be COR₆ or COCOR₆ when W is CO;

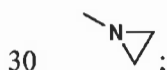
20 wherein Q₁ is selected from the group of heteroaryl, substituted heteroaryl, halogen,
 -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₁₀R₁₁ and -SO₂R₇;

R_5 is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted
 alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₁₀, -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

25

with the proviso that only one of R_4 or R_5 can be selected from the group of -COR₆,
 -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

or when W is absent or is CH₂, then R_4 and R_5 can be taken together with the adjacent N
 to form



R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

5

wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

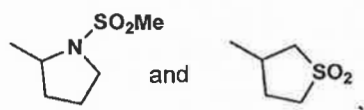
R₇ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -CF₃, aryl, and heteroaryl;

10

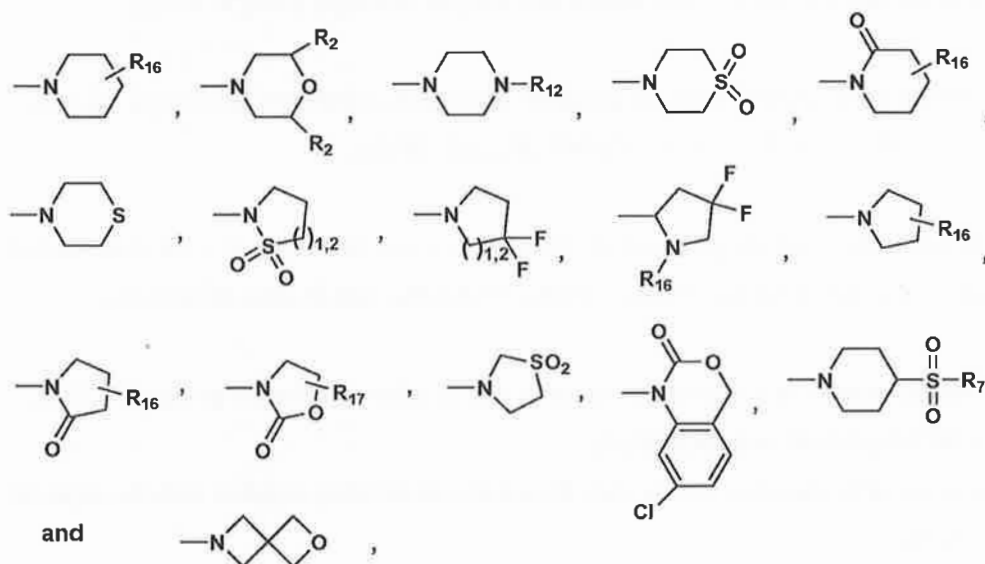
R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,

15

and R₈ and R₉ can also be independently selected from the group of



or R₈ and R₉ are taken together with the adjacent N to form a cycle selected from the group of:

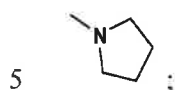


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with the proviso that only one of R₈ or R₉ can be -COOR₃;

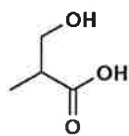
R_{10} and R_{11} are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl and -C₃₋₆ cycloalkyl,

or R_{10} and R_{11} are taken together with the adjacent N to form a cycle such as



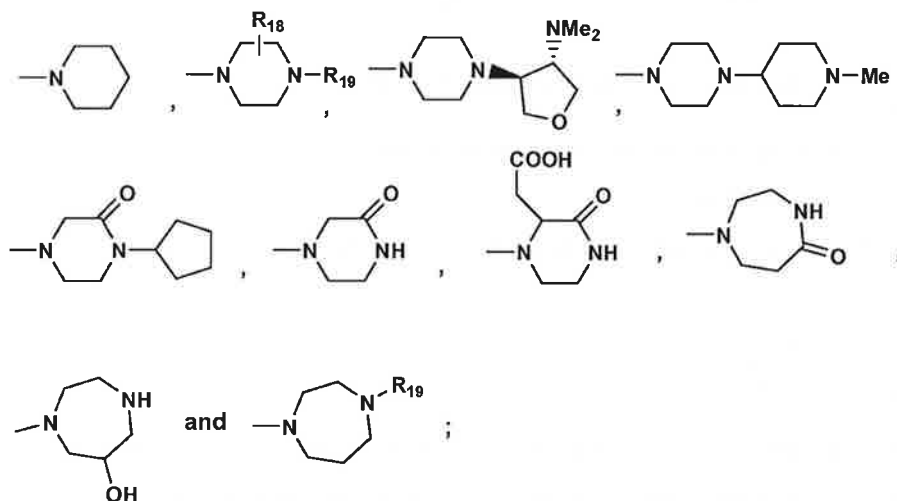
R_{12} is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ alkyl-OH; -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -COR₇, -COONR₂₂R₂₃, -SOR₇, and -SONR₂₄R₂₅;

- 10 R_{13} and R_{14} are independently selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃, C₁₋₆ substituted alkyl-Q₃ and



or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the

15 group of:



Q_3 is selected from the group of heteroaryl, substituted heteroaryl, -NR₂₀R₂₁, -CONR₂R₂, -COOR₂, -OR₂, and -SO₂R₃;

R₁₅ is selected from the group of -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃ and -C₁₋₆ substituted alkyl-Q₃;

R₁₆ is selected from the group of -H, -C₁₋₆ alkyl, -NR₂R₂, and -COOR₃;

5

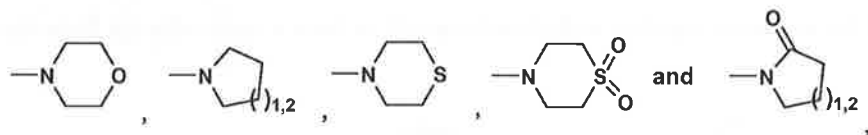
R₁₇ is selected from the group of -H, -C₁₋₆ alkyl, -COOR₃, and aryl;

R₁₈ is selected from the group of -COOR₂ and -C₁₋₆ alkyl-COOR₂;

- 10 R₁₉ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₄, -COR₃, -COOR₃, wherein Q₄ is selected from the group of -NR₂R₂ and -OR₂;

R₂₀ and R₂₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ substituted alkyl-OR₂, and -COR₃,

- 15 or R₂₀ and R₂₁ are taken together with the adjacent N to form a cycle selected from the group of

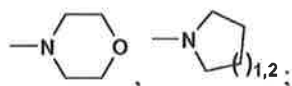


with the proviso that only one of R₂₀ or R₂₁ can be -COR₃;

20

R₂₂ and R₂₃ are independently selected from the group of H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, and -C₁₋₆ cycloalkyl,

or R₂₂ and R₂₃ are taken together with the adjacent N to form a cycle selected from the group of



25

R₂₄ and R₂₅ are independently from the group of H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₅, -C₁₋₆ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and Q₅ is selected from the group of halogen and SO₂R₃.

30

Even more preferred compounds include those wherein R₁ is isopropenyl.

Also preferred are compounds wherein W is absent.

Also preferred compounds include those which are encompassed by Formula I. Of these, those wherein X is a C₄₋₈ cycloalkenyl, C₄₋₉ spirocycloalkyl or C₄₋₉ spirocycloalkenyl group are even more preferred.

5

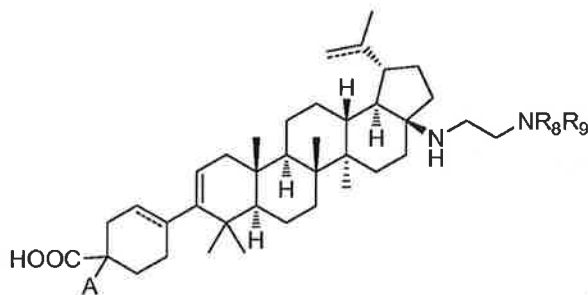
Also preferred are compounds of Formula I wherein Y is in the para position.

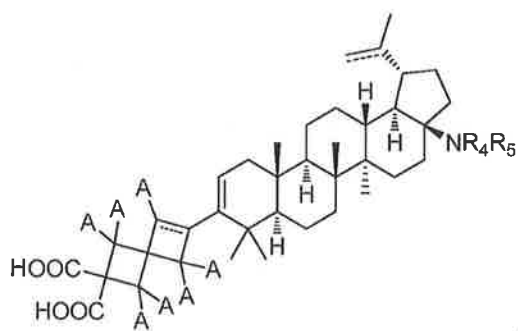
Also preferred are compounds of Formula I wherein A is at least one member selected from the group of -H, -OH, -halo, -C₁₋₃ alkyl, and -C₁₋₃ alkoxy, wherein -halo is
10 selected from the group of -Cl, -F and -Br, with -F being more preferred. It is even more preferred that A is -H.

Also preferred are compounds of Formula I wherein Y is -COOR₂, and more preferably -COOH.

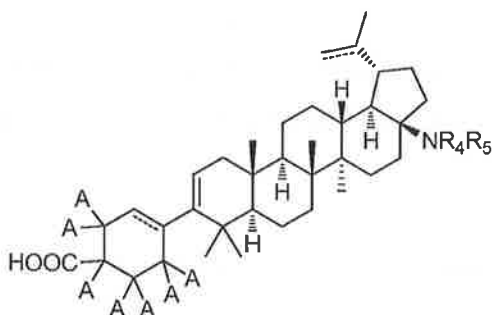
15

A preferred class of compounds, including pharmaceutically acceptable salts thereof, includes the following structures:

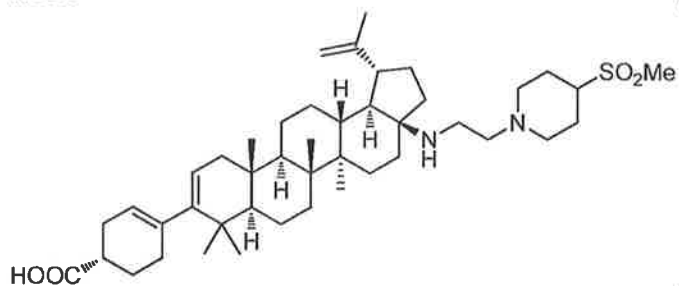
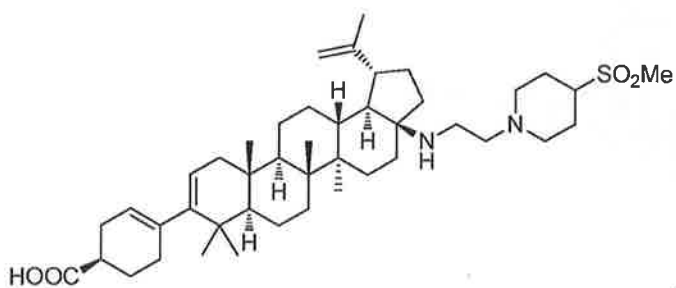


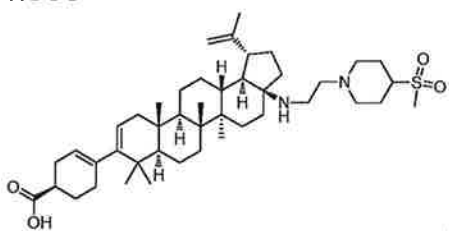
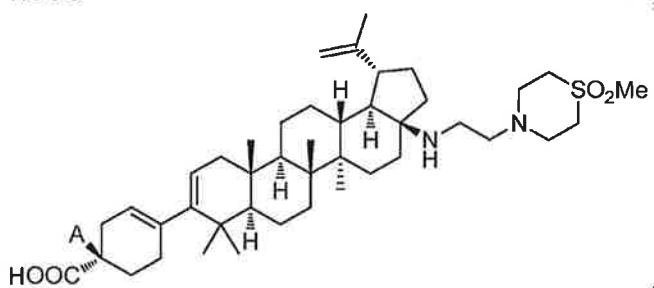
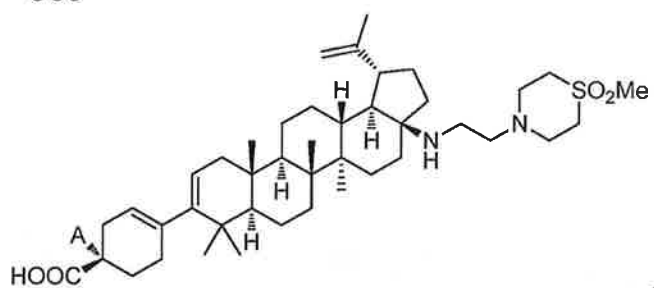
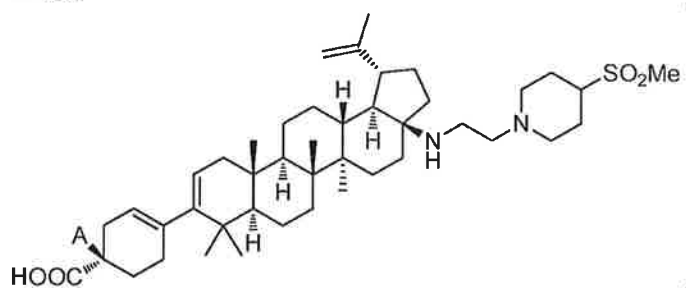
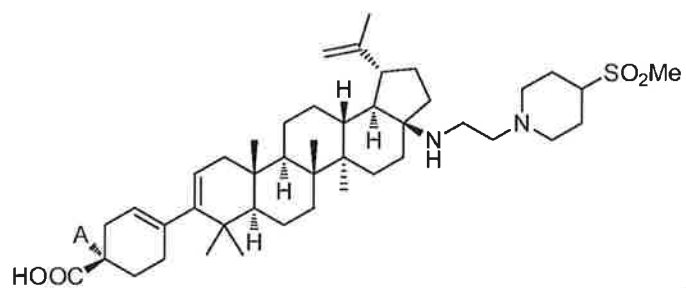


, and

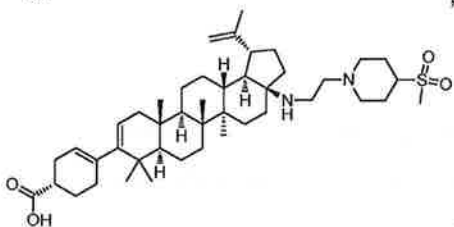


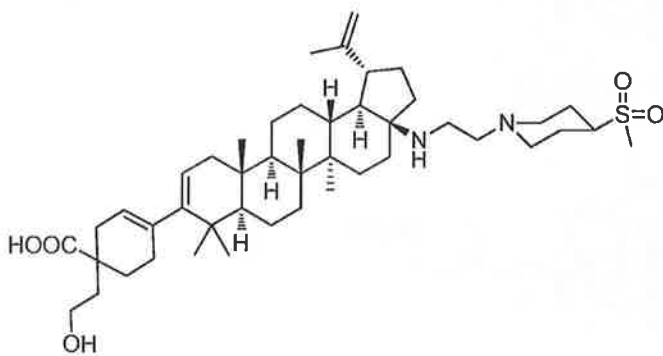
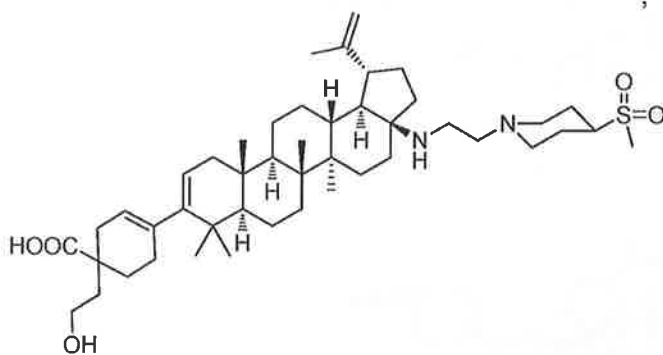
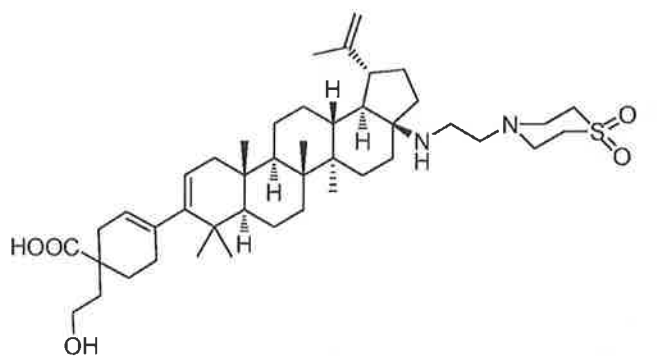
Other compounds, including pharmaceutically acceptable salts thereof, which are
 5 preferred as part of the invention include the following:



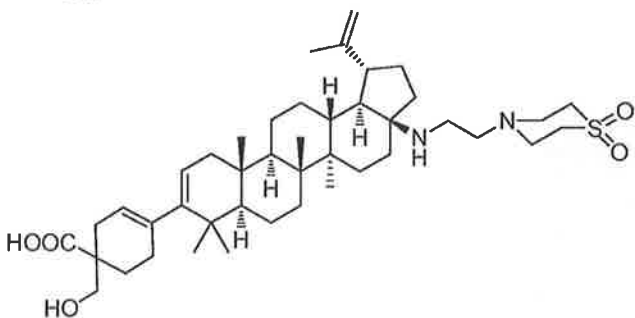


5





, and



5

The compounds of the present invention, according to all the various embodiments described above, may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion

techniques), by inhalation spray, or rectally, and by other means, in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, excipients and diluents available to the skilled artisan. One or more adjuvants may also be included.

5 Thus, in accordance with the present invention, there is further provided a method of treatment, and a pharmaceutical composition, for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition which contains an antiviral effective amount of one or more of the compounds of Formulas I, II, and/or III, together with one or more
10 pharmaceutically acceptable carriers, excipients or diluents. As used herein, the term "antiviral effective amount" means the total amount of each active component of the composition and method that is sufficient to show a meaningful patient benefit, i.e., inhibiting, ameliorating, or healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the
15 term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing, ameliorating or healing diseases associated with HIV infection.

20

 The pharmaceutical compositions of the invention may be in the form of orally administrable suspensions or tablets; as well as nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories. Pharmaceutically acceptable carriers, excipients or diluents may be
25 utilized in the pharmaceutical compositions, and are those utilized in the art of pharmaceutical preparations.

 When administered orally as a suspension, these compositions are prepared according to techniques typically known in the art of pharmaceutical formulation and may
30 contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose

and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

5 The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

10 The compounds herein set forth can be administered orally to humans in a dosage range of about 1 to 100 mg/kg body weight in divided doses, usually over an extended period, such as days, weeks, months, or even years. One preferred dosage range is about 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is about 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that
15 the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

20 Also contemplated herein are combinations of the compounds of Formulas I, II, III and /or IV herein set forth, together with one or more other agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination
25 with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following non-limiting table:

ANTIVIRALS

	<i>Drug Name</i>	<i>Manufacturer</i>	<i>Indication</i>
5	097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse trans- criptase (RT) inhibitor)
10			
	Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
15			
	Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
20	Acemannan	Carrington Labs (Irving, TX)	ARC
	Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC
25			
	AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
	AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
30			
	Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
35			
	Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
40	Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC

5	Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
	AR177	Aronex Pharm	HIV infection, AIDS, ARC
10	Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
15	BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
	CI-1012	Warner-Lambert	HIV-1 infection
20	Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
	Curdlan sulfate	AJI Pharma USA	HIV infection
25	Cytomegalovirus Immune globulin	MedImmune	CMV retinitis
	Cytovene	Syntex	Sight threatening
30	Ganciclovir		CMV peripheral CMV retinitis
	Darunavir	Tibotec- J & J	HIV infection, AIDS, ARC (protease inhibitor)
35	Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
40	Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
	ddC	Hoffman-La Roche	HIV infection, AIDS,

	Dideoxycytidine		ARC
5	ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
10	DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
15	Efavirenz (DMP 266, Sustiva®) (-)-6-Chloro-4-(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
20	EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
25	Etravirine	Tibotec/ J & J	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
30	Famciclovir	Smith Kline	herpes zoster, herpes simplex
35	GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
40	HBV097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
	Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
45	Recombinant Human	Triton Biosciences	AIDS, Kaposi's

	Interferon Beta	(Alameda, CA)	sarcoma, ARC
	Interferon alfa-n3	Interferon Sciences	ARC, AIDS
5	Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
10	ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
	KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
15	Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
20	Lobucavir	Bristol-Myers Squibb	CMV infection
25	Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
30	Nevirapine	Boehringer Ingelheim	HIV infection, AIDS, ARC (RT inhibitor)
	Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
35	Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
40	Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
	PNU-140690	Pharmacia Upjohn	HIV infection,

			AIDS, ARC (protease inhibitor)
5	Probucol	Vyrex	HIV infection, AIDS
	RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
10	Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
15	Saquinavir	Hoffmann- LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
20	Stavudine; d4T Didehydrodeoxy- Thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
	Tipranavir	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
25	Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
	Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
30	VX-478	Vertex	HIV infection, AIDS, ARC
	Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
35	Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
40	Tenofovir disoproxil, fumarate salt (Viread [®])	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)

	Emtriva [®] (Emtricitabine) (FTC)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
5	Combivir [®]	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
10	Abacavir succinate (or Ziagen [®])	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
15	Reyataz [®] (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDS, protease inhibitor
20	Fuzeon [®] (Enfuvirtide or T-20)	Roche / Trimeris	HIV infection AIDS, viral Fusion inhibitor
25	Lexiva [®] (or Fosamprenavir calcium)	GSK/Vertex	HIV infection AIDS, viral protease inhibitor
30	Selzentry Maraviroc; (UK 427857)	Pfizer	HIV infection AIDS, (CCR5 antagonist, in development)
35	Trizivir [®]	GSK	HIV infection AIDS, (three drug combination)
	Sch-417690 (vicriviroc)	Schering-Plough	HIV infection AIDS, (CCR5 antagonist, in development)
40	TAK-652	Takeda	HIV infection AIDS, (CCR5 antagonist, in development)

	GSK 873140 (ONO-4128)	GSK/ONO	HIV infection AIDs, (CCR5 antagonist, in development)
5	Integrase Inhibitor MK-0518 Raltegravir	Merck	HIV infection AIDs
10	Truvada [®]	Gilead	Combination of Tenofovir disoproxil fumarate salt (Viread [®]) and Emtriva [®] (Emtricitabine)
15	Integrase Inhibitor GS917/JTK-303 Elvitegravir	Gilead/Japan Tobacco	HIV Infection AIDs in development
20	Triple drug combination Atripla [®]	Gilead/Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (Viread [®]), Emtriva [®] (Emtricitabine), and Sustiva [®] (Efavirenz)
25	Festinavir [®] 4'-ethynyl-d4T	Oncolys BioPharma BMS	HIV infection AIDs in development
30	CMX-157 Lipid conjugate of nucleotide tenofovir	Chimerix	HIV infection AIDs
35	GSK1349572 Integrase inhibitor	GSK	HIV infection AIDs

IMMUNOMODULATORS

	<i>Drug Name</i>	<i>Manufacturer</i>	<i>Indication</i>
40	AS-101	Wyeth-Ayerst	AIDS
	Bropirimine	Pharmacia Upjohn	Advanced AIDS

	Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
5	CL246,738	Wyeth Lederle Labs	AIDS, Kaposi's sarcoma
	FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
10	Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
15	Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
20	Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
25	Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
	HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
30	IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
	IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
35	IL-2 Interleukin-2 (aldeslakin)	Chiron	AIDS, increase in CD4 cell counts
40	Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT

	IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
5	IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
	Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
10	Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
	Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
15	MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
20	Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
	Remune	Immune Response Corp.	Immunotherapeutic
25	rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
30	rCD4-IgG hybrids		AIDS, ARC
	Recombinant Soluble Human CD4	Biogen	AIDS, ARC
35	Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
40	SK&F106528 Soluble T4	Smith Kline	HIV infection
	Thymopentin	Immunobiology Research Institute	HIV infection

	Tumor Necrosis Factor; TNF	(Annandale, NJ) Genentech	ARC, in combination w/gamma Interferon
5	ANTI-INFECTIVES		
	<i>Drug Name</i>	<i>Manufacturer</i>	<i>Indication</i>
10	Clindamycin with Primaquine	Pharmacia Upjohn	PCP
15	Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
	Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
20	Ornidyl Eflornithine	Merrell Dow	PCP
	Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
25	Trimethoprim		Antibacterial
	Trimethoprim/sulfa		Antibacterial
30	Piritrexim	Burroughs Wellcome	PCP treatment
	Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
35	Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
	Intraconazole- R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal

			meningitis
	Trimetrexate	Warner-Lambert	PCP
5	Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
	Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
10	Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
15	Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
	Testosterone	Alza, Smith Kline	AIDS-related wasting
20	Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the disclosure herein set forth may be used in
 25 combination with HIV entry inhibitors. Examples of such HIV entry inhibitors are
 discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp.
 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp.
 183-194 and *Inhibitors of the entry of HIV into host cells*. Meanwell, Nicholas A.;
 Kadow, John F., Current Opinion in Drug Discovery & Development (2003), 6(4),
 30 451-461. Specifically the compounds can be utilized in combination with attachment
 inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the
 CCR5 or CXCR4 coreceptor. HIV attachment inhibitors are also set forth in US
 7,354,924 and US 7,745,625.

35 It will be understood that the scope of combinations of the compounds of this
 application with AIDS antivirals, immunomodulators, anti-infectives, HIV entry
 inhibitors or vaccines is not limited to the list in the above Table but includes, in

principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a
5 compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is Reyataz[®] (active ingredient Atazanavir). Typically a dose of 300 to 600mg is administered once a day. This may be
10 co-administered with a low dose of Ritonavir (50 to 500mgs). Another preferred inhibitor of HIV protease is Kaletra[®]. Another useful inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentanamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is
15 generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV.
20 Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) tenofovir disoproxil fumarate salt and emtricitabine.

25 In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

GENERAL CHEMISTRY (METHODS OF SYNTHESIS)

The present invention comprises compounds of Formulas I, II, III, and IV their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formulas I, II, III, and IV also include pharmaceutically acceptable salts thereof. General procedures to construct compounds of Formulas I, II, III and IV and intermediates useful for their synthesis are described in the following Schemes (after the Abbreviations).

Abbreviations

10

One or more of the following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, may be used throughout the description of the disclosure and the examples:

15 Bz₂O = benzoic anhydrideTBTU = O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

20 HATU = 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium

DCE = dichloroethane

DCM = dichloromethane

25

CDI = carbonyl diimidazole

prep. HPLC = preparative high performance liquid chromatography

30 rt = room temperature

DIPEA = diisopropylethylamine

DMAP = 4-dimethylaminopyridine

35

DMSO = dimethylsulfoxide

THF = tetrahydrofuran

40 KHMDs = potassium bis(trimethylsilyl)amide

min = minute(s)

h = hour(s)

5 sat. = saturated

TEA = triethylamine

EtOAc = ethyl acetate

10

TFA = trifluoroacetic acid

PCC = pyridinium chlorochromate

15 TLC = thin layer chromatography

Tf₂NPh = (trifluoromethylsulfonyl)methanesulfonamide

dioxane = 1,4-dioxane

20

PG = protective group

atm = atmosphere(s)

25 mol = mole(s)

mmol= milimole(s)

mg = milligram(s)

30

μg = microgram(s)

μl = microliter(s)

35 μm= micrometer(s)

mm= millimeter(s)

HOAc= acetic acid

40

MeOH= methanol

DMF= *N,N*-dimethylformamide

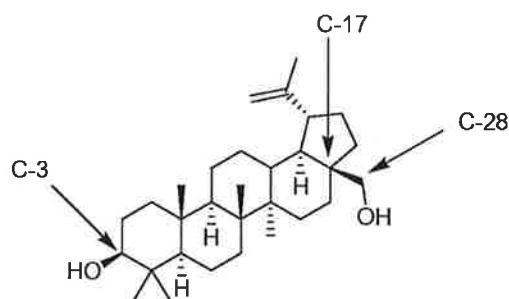
45 TBAF= tetrabutylammonium fluoride

TBDMSCl= *tert*-butyldimethylsilyl chloride

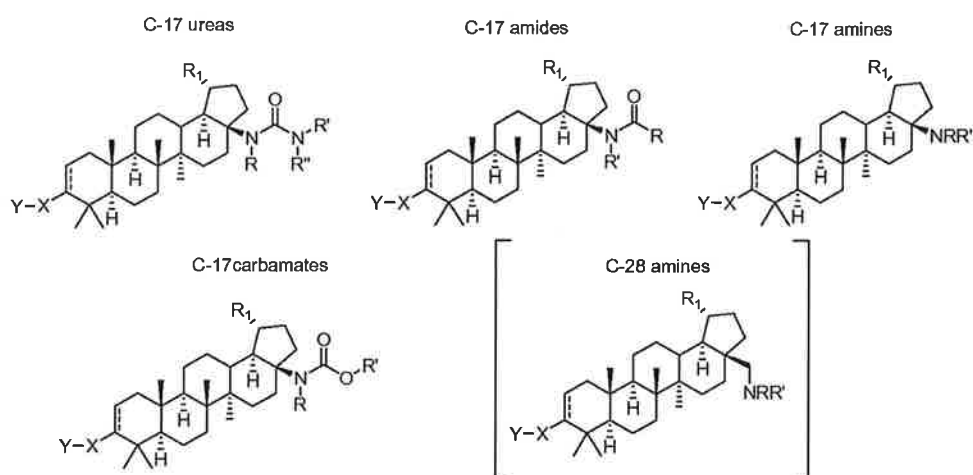
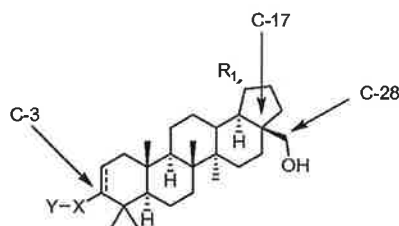
RBF = round bottom flask

DI= deionized

The terms "C-3" and "C-28" refer to certain positions of a triterpene core as numbered in accordance with IUPAC rules (positions depicted below with respect to an illustrative triterpene: betulin):



The same numbering is maintained when referring to the compound series in schemes and general descriptions of methods.



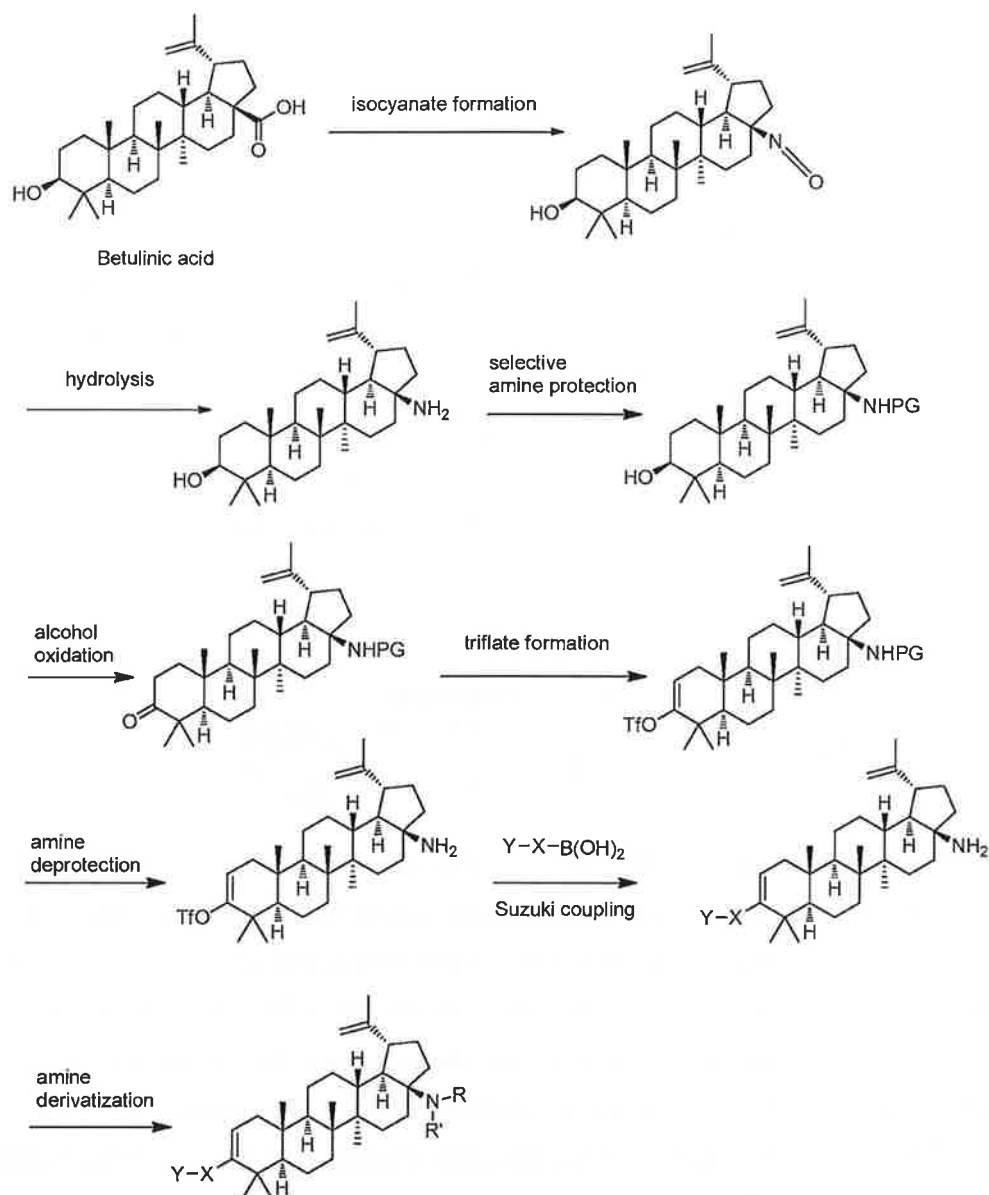
Preparation of Compounds of Formulas I, II, III and IV General Chemistry Schemes:

Preparation of Compounds of Formulas I, II, III and IV General Chemistry Schemes:

- 5 Compounds of Formula I can be prepared from commercially available (Aldrich, others) betulinic acid by chemistry described in the following schemes. Compounds of Formula II, III and IV are described thereafter.

General reaction schemes are set forth as follows:

Scheme 1

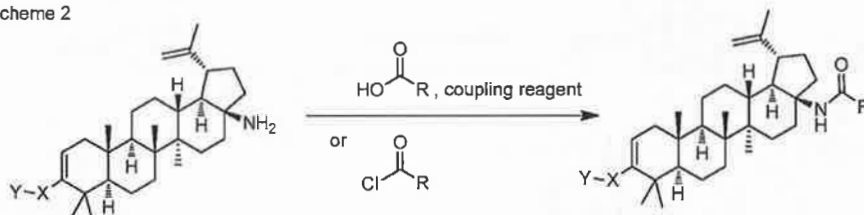


Compounds of formula I can be prepared from betulinic acid as described in Scheme 1. Curtis rearrangement of betulinic acid can be accomplished without protection of the C-3 hydroxyl group to render the C-17 isocyanate which upon acid hydrolysis affords the C-17 amine. The C-17 amine is then selectively protected with an amine protective group (i.e F-moc, Boc) to then perform the oxidation of the C-3 hydroxy group to a ketone under standard conditions (i.e. PCC, Dess-Martin reagent, etc). Conversion of the ketone into its triflate can be accomplished by methods known to those skilled in the art. The

protective group in the amino group is then taken off to produce the C-17 unsubstituted amine. Installation of the C-3 moiety is accomplished via Suzuki coupling of the triflate with the corresponding boronic acid as described above. Alternatively, the triflate coupling with the corresponding boronic acid can be performed before the deprotection of the C-17 amine. Once deprotected, the C-17 amino group can then be further derivatized by methods known to those skilled in the art such as alkylation, reductive amination, acylation, etc. Several of these methods are described in the Schemes below (Scheme 2-7). In some cases, an additional step is needed to unmask any functional group that may be functionalized with a protective group (i.e. when Y is COOH, is always masked as the corresponding ester COOR until this last step).

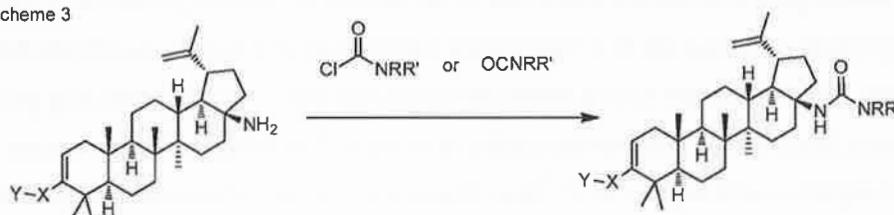
The C-17 primary amine can be further modified using standard methods, known to those skilled in the art. Some examples are shown in the following schemes.

Scheme 2



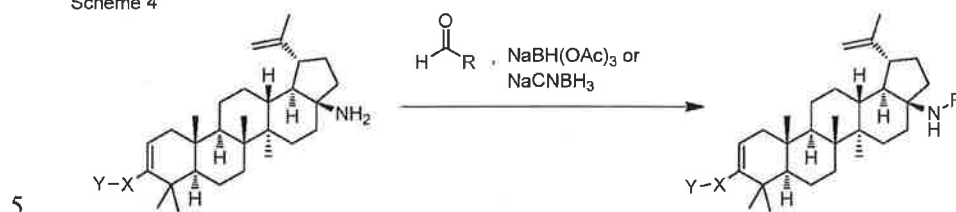
C-17 amides can be prepared by reacting a carboxylic acid with the C-17 primary amine in the presence of an adequate coupling reagent such as HATU, DCC, and others known to those skilled in the art, in the presence of a base such as Hunig's base, TEA, etc., in the appropriate solvent (DCM, THF, DMF, etc.). Hydrolysis of the carboxylic ester affords the benzoic acid. Alternatively, some amides can be prepared by treating the C-17 primary amine with the corresponding carboxylic acid chloride reagent instead of an acid. Similarly, sulfonamides and sulfonamides can be prepared from the C-17 primary amine by using a sulfonyl chloride as the sulfonylating agent.

Scheme 3



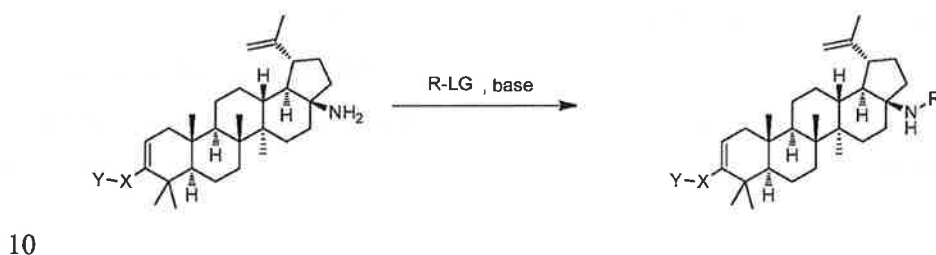
C-17 ureas can be prepared by reacting the corresponding carbamoyl chloride or isocyanate in the presence of a base such as Hunig's base, TEA, etc., in the appropriate solvent (DCM, THF, DMF, etc.). C-17 carbamates can be prepared in a similar manner using a chloroformate instead of the carbamoyl chloride.

Scheme 4



The C-17 primary amine can be treated with an aldehyde under reductive amination conditions (e.g. NaBH(OAc)₃) in the presence of AcOH/NaOAc or Ti(OPr)₄ in a solvent such as THF, 1,4-dioxane, DCE or DCM) to afford C-17 secondary amines.

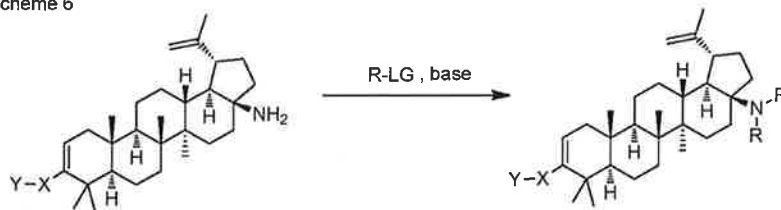
Scheme 5



Some C-17 amines can be prepared by alkylation of the C-17 primary amine with an alkylating agent (R-LG), where LG is a leaving group such as, but not limited to Br, Cl, I, mesylate, tosylate or triflate in the presence of a base. Heating may be needed in some cases. Hydrolysis of the carboxylic ester renders the benzoic acid product.

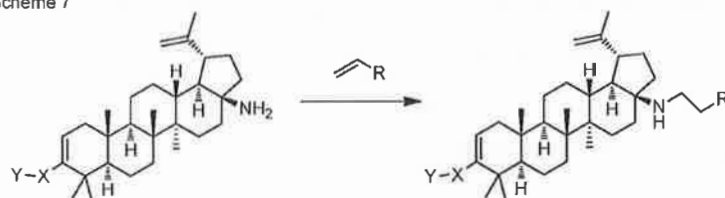
15

Scheme 6



In some cases, by prolonging the reaction times and heating the reaction mixture, the dialkylated product can also be formed.

Scheme 7



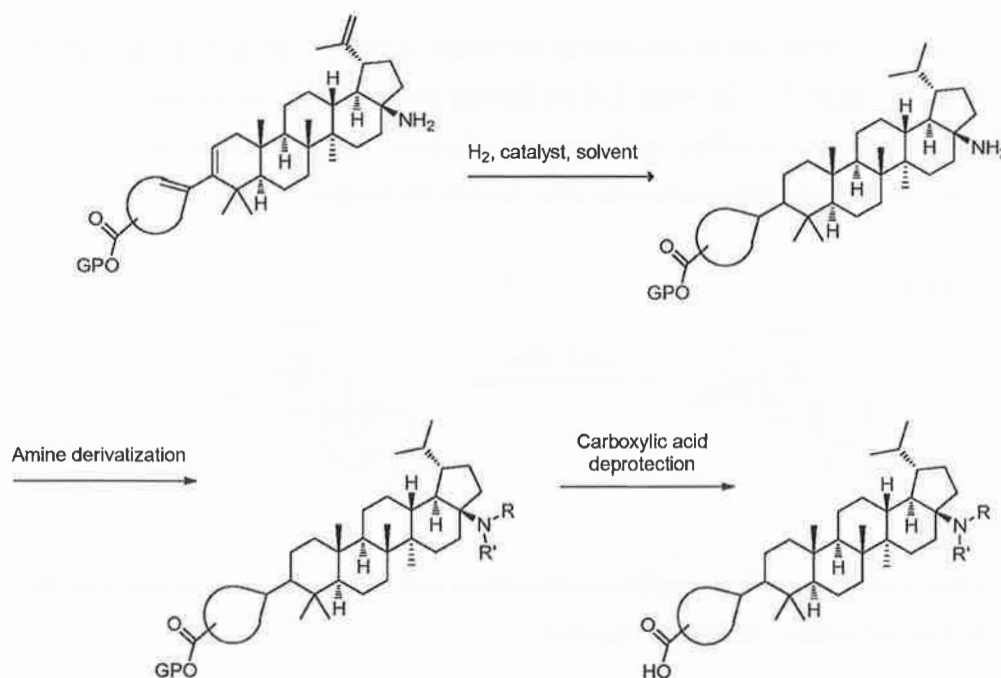
Alternatively, some C-17 amines can be prepared by 1,4-addition to Michael acceptors.

- Substituents R, R' and R'' may contain functional groups (i.e. COOH, COOR, OH, NHR) that can be further modified by methods known to those skilled in the art. The modification can be carried out before or after the final deprotection of the carboxylic acid is performed depending on the nature of the functional group.

- Alternatively, the C-17 secondary amine can be further modified (i.e. alkylated, acylated, sulfonylated, etc.) using some of the methods described above or other standard methods known to those skilled in the art.

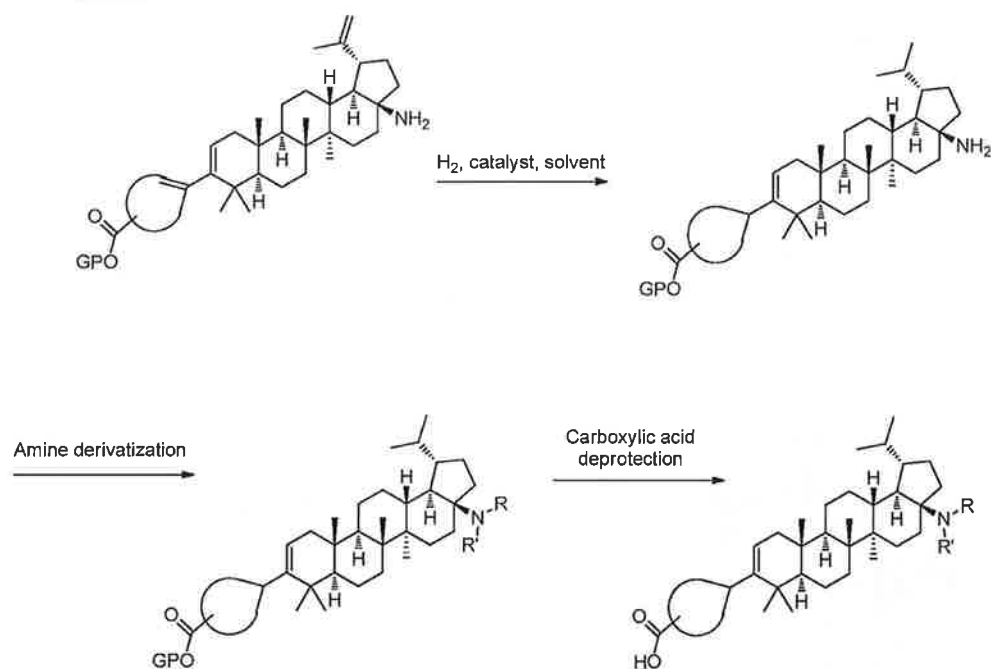
Compounds of formula II can be prepared using the chemistry methods described above for compounds of formula I, with one extra step which consists of saturation of the double bonds as shown in scheme 8.

Scheme 8



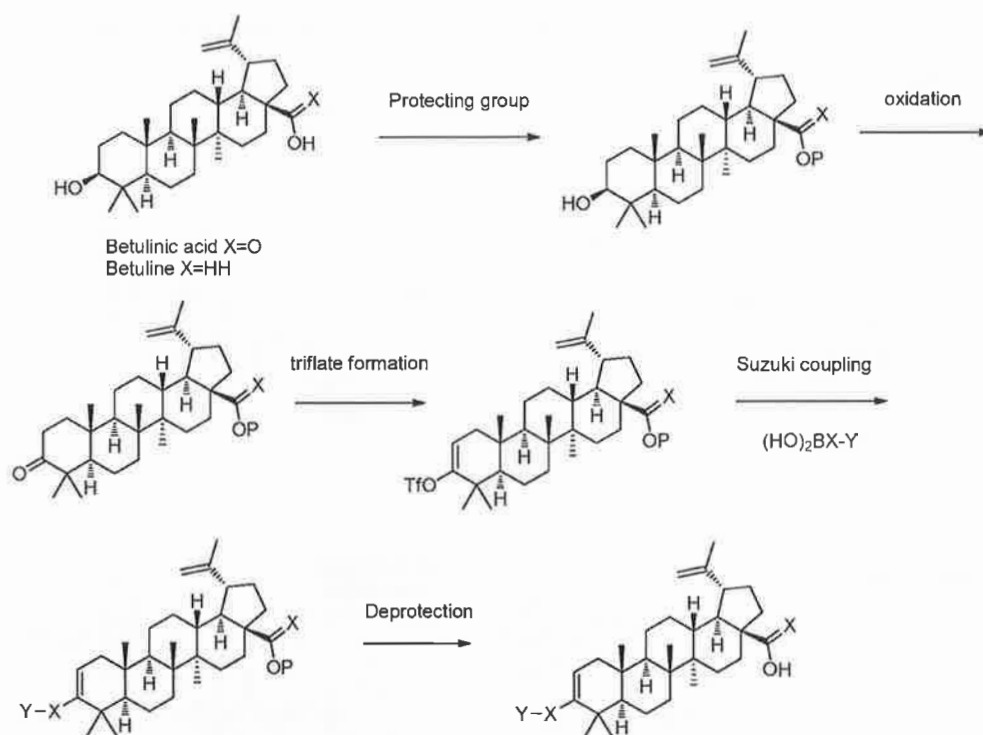
Alternatively, the hydrogenation of the olefins can be controlled to preserve the A-ring unsaturation as shown in scheme 9.

Scheme 9



- 5 Compounds of formula III can be prepared in the same manner described above for compounds of formula I and II using oleanoic or ursolic acid as starting materials instead of betulinic acid.

Compounds of formula IV can be prepared from betuline or betulinic acid as described in the scheme below:



EXAMPLES

- 5 The following examples illustrate typical syntheses of the compounds of Formulas I, II, III and IV as described generally above. These examples are illustrative only and are not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

10 Chemistry

Typical Procedures and Characterization of Selected Examples:

- 15 Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ¹H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker AV 400 MHz, Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The

chemical shifts were reported in ppm on the δ scale relative to $\delta\text{TMS} = 0$. The following internal references were used for the residual protons in the following solvents: CDCl_3 (δ_{H} 7.26), CD_3OD (δ_{H} 3.30), Acetic- d_4 (*Acetic Acid d_4*) (δ_{H} 11.6, 2.07), DMSO mix or DMSO- D_6 - CDCl_3 (δ_{H} 2.50 and 8.25) (ratio 75%:25%), and DMSO- D_6 (δ_{H} 2.50).

- 5 Standard acronyms were employed to describe the multiplicity patterns: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (J) is in Hertz. All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for
- 10 LC in electrospray mode.

LC/MS methods:

Method 1

- 15 Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
- 20 Column = Phenomenex Luna C18, 3 μm , 2.0 x 30 mm

Method 2

- Start %B = 0, Final % B = 100 over 2 minute gradient, hold at 100% B
Flow Rate = 1 mL / Min
- 25 Wavelength = 220 nm
Solvent A = 90% Water, 10% methanol/ 0.1% TFA
Solvent B = 10% Water, 90% methanol/ 0.1% TFA
Column = Phenomenex Luna C18, 3 μm , 2.0 x 30 mm

30 Method 3

Start %B = 0, Final % B = 100 over 2 minute gradient , hold at 100% B
Flow Rate = 1 mL / Min

Wavelength = 220 nm

Solvent A = 95% Water, 5% methanol/ 10 Mm ammonium acetate

Solvent B = 5% Water, 95% methanol/ 10 Mm ammonium acetate

Column = Phenomenex Luna C18, 3 μ m, 2.0 x 30 mm

5

Method 4:

Start % B = 30, Final % B = 100, gradient Time = 2 min

Flow Rate = 0.8 mL/min

Wavelength = 220

10 Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = Xbridge Phenyl 2.1 X 50 mm 2.5 μ m

Method 5:

15 Start % B = 30, Final % B = 100, gradient Time = 2 min

Flow Rate = 1 mL/min

Wavelength = 220

Solvent A = 5% MeOH - 95% H₂O - 10mM NH₄OAc

Solvent B = 95% MeOH - 5% H₂O - 10mM NH₄OAc

20 Column = Phenomenex LUNA C₁₈ 2.0 X 30 mm 3 μ m

Method 6:

Start % B = 0, Final % B = 100, gradient Time = 4 min

Flow Rate = 0.8 mL/min

25 Wavelength = 220

Solvent Pair = MeOH:H₂O:(0.1% TFA)

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = Xbridge Phenyl 2.1 x 50 mm 2.5 μ m

30

Method 7:

Start % B = 10, Final % B = 100, gradient Time = 3 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 5% MeOH - 95% H₂O - 10mM NH₄OAc

Solvent B = 95% MeOH - 5% H₂O - 10mM NH₄OAc

- 5 Column = Phenomenex LUNA C₁₈ 2.0 X 50 mm 3μm

Method 8:

Start % B = 20, Final % B = 100, gradient Time = 2 min

Flow Rate = 0.8 mL/min

- 10 Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = Xbridge Phenyl 2.1 X 50 mm 2.5μm

- 15 Method 9:

Start % B = 50, Final % B = 100, gradient Time = 6 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

- 20 Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-LUNA 2.0 X 50mm 3μm

Method 10:

Start % B = 30, Final % B = 100, gradient Time = 3 min

- 25 Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

- 30

Method 11:

Start % B = 0, Final % B = 100, gradient Time = 4 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

- 5 Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

Method 12:

Start % B = 40, Final % B = 100, gradient Time = 4 min

Flow Rate = 0.8 mL/min

- 10 Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

- 15 Method 13:

Start % B = 50, Final % B = 100, gradient Time = 4 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

- 20 Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

Method 14:

Start % B = 75, Final % B = 100, gradient Time = 2 min

- 25 Flow Rate = 1.0 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 30mm 3μm

- 30

Method 15:

Start % B = 50, Final % B = 90, gradient Time = 4 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

- 5 Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

Method 16:

Start % B = 50, Final % B = 100, gradient Time = 3 min

Flow Rate = 0.8 mL/min

- 10 Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

- 15 Method 17:

Start % B = 25, Final % B = 100, gradient Time = 2 min

Flow Rate = 1.0 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

- 20 Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 30mm 3μm

Method 18:

Start % B = 50, Final % B = 100, gradient Time = 4 min

- 25 Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 30mm 3μm

30

Method 19:

Start % B = 50, Final % B = 100, gradient Time = 4 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

- 5 Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

Method 20:

Start % B = 0, Final % B = 80, gradient Time = 4 min

Flow Rate = 0.8 mL/min

- 10 Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

- 15 Method 21:

Start % B = 0, Final % B = 100, gradient Time = 3 min

Flow Rate = 0.8 mL/min

Wavelength = 220

Solvent A = 10% MeOH - 90% H₂O(0.1% TFA)

- 20 Solvent B = 90% MeOH - 10% H₂O(0.1% TFA)

Column = PHENOMENEX-C₁₈ 2.0 X 50mm 3μm

Prep HPLC

- 25

Method 1

Start %B = 25 Final %B = 100 over 10 minute gradient, hold at 100% B

Flow Rate = 25 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

- 30 Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = X-bridge Phenyl 19x100 mm 5μm

Method 2

Start %B = 25 Final %B = 100 over 12 minute gradient, hold at 100% B

Flow Rate = 25 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

5 Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = X-bridge Phenyl 19x100 mm 5μm

Method 3

Start %B = 30 Final %B = 100 over 12 minute gradient, hold at 100% B

10 Flow Rate = 25 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = X-bridge Phenyl 19x100 mm 5μm

15 Method 4

Start %B = 15 Final %B = 100 over 20 minute gradient, hold at 100% B

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

20 Column = Waters Sunfire 30 x 100 mm 5μm

Method 5

Start %B = 15 Final %B = 100 over 15 minute gradient, hold at 100% B

Flow Rate = 40 mL/min

25 Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5μm

Method 6

30 Start %B = 20 Final %B = 80 over 20 minute gradient

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5μm

5 Method 7

Start %B = 20 Final %B = 75 over 25 minute gradient

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

10 Column = Waters Sunfire 30 x 100 mm 5μm

Method 8

Start %B = 25 Final %B = 90 over 15 minute gradient

Flow Rate = 40 mL/min

15 Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5μm

Method 9

20 Start %B = 25 Final %B = 80 over 20 minute gradient

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5μm

25

Method 10

Start %B = 20 Final %B = 100 over 15 minute gradient

Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

30 Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5 μ m

Method 11

Start %B = 10 Final %B = 85 over 12 minute gradient

5 Flow Rate = 40 mL/min

Solvent A = 10% ACN - 90% H₂O - 0.1% TFA

Solvent B = 90% ACN - 10% H₂O - 0.1% TFA

Column = Waters Sunfire 30 x 100 mm 5 μ m

10 Method 12

Start %B = 40 Final %B = 100 over 12 minute gradient, hold at 100% B

Flow Rate = 25 mL/min

Solvent A = 5% MeOH - 95% H₂O - 10 mM ammonium acetate

Solvent B = 95% MeOH - 5% H₂O - 10 mM ammonium acetate

15 Column = X-bridge Phenyl 19x100 mm 5 μ m

Method 13:

Start % B = 10, Final % B = 100, gradient Time = 10 min

Flow Rate = 25 mL/min

20 Wavelength = 220

Solvent A = 5% MeCN - 95% H₂O - 10mM NH₄OAc

Solvent B = 95% MeCN - 5% H₂O - 10mM NH₄OAc

Column = Xbridge OBD Prep Shield RP-18 19 X 100 mm 5 μ m

25 Method 14:

Start % B = 10, Final % B = 100, gradient Time = 10 min

Flow Rate = 25 mL/min

Wavelength = 220

Solvent A = 5% MeCN - 95% H₂O - 10mM NH₄OAc

30 Solvent B = 95% MeCN - 5% H₂O - 10mM NH₄OAc

Column = Xbridge Prep C₁₈ 19 X 100 mm 5 μ m

Method 15:

Start % B = 10, Final % B = 100, gradient Time = 10 min

Flow Rate = 40 mL/min

Wavelength = 220

5 Solvent A = 10% MeCN - 90% H₂O(0.1% TFA)

Solvent B = 90% MeCN - 10% H₂O(0.1% TFA)

Column = WATERS-Sunfire 30 X 100 mm S5

Method 16:

Start % B = 10, Final % B = 90, gradient Time = 15 min

10 Flow Rate = 40 mL/min

Wavelength = 220

Solvent A = 10% MeCN - 90% H₂O(0.1% TFA)

Solvent B = 90% MeCN - 10% H₂O(0.1% TFA)

Column = Waters-Sunfire 30 X 100 mm S5

15

Chiral SFC Method 1

Column: ChiralCel OJ-H, 30 x 250mm, 5μm

Mobile Phase: 10 % EtOH (w/15mM NH₃) / 90% CO₂

Pressure: 120 bar

20 Temperature: 35°C

Flow Rate: 70 mL/min

UV: 205 nm

Injection: 0.5 mL (~10mg/mL in CH₃Cl:EtOH (9:1)) stacked @ 6.5' intervals

25 Fraction Collection: Peak 1:14.25' - 15.50'

Peak 2:15.70' - 17.80'

Chiral SFC Method 2

Column: ChiralCel OJ-H, 30 x 250mm, 5μm

30 Mobile Phase: 30 % MeOH / 70% CO₂

Pressure: 100 bar

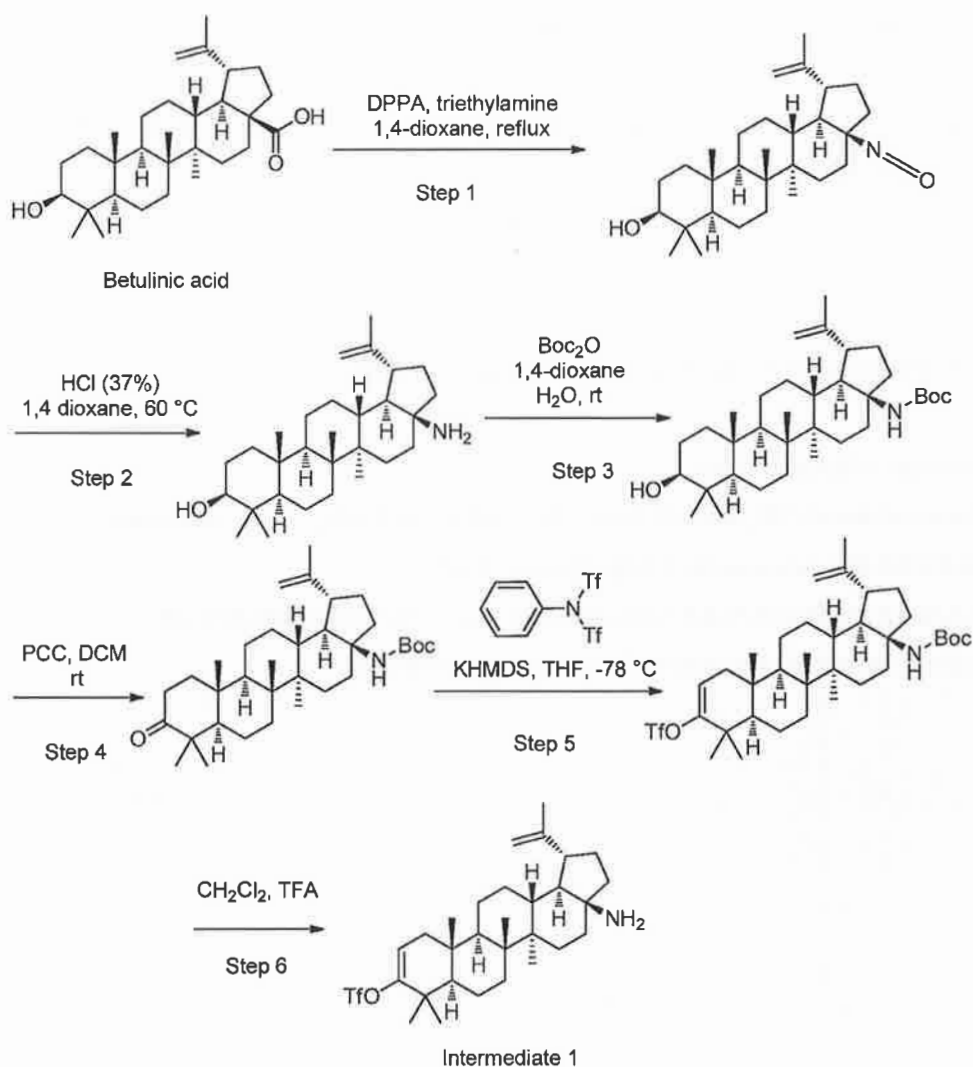
Temperature: 35°C

Flow Rate:	70 mL/min
UV:	210 nm
Injection:	0.4 mL (~500 mg/mL in MeOH) @ 7.70' intervals
Fraction Collection:	Peak 1: 4.45' - 5.65'
5	Peak 2: 5.90' - 9.40'

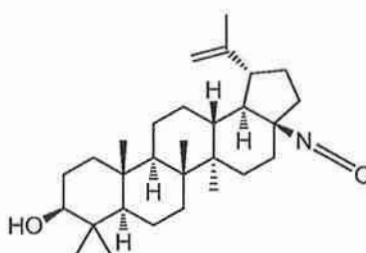
Key intermediate 1 was prepared by the following methods:

10 **Method 1: Intermediate 1**

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

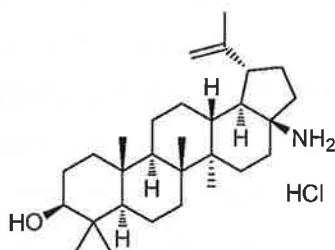


Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol



To a suspension of betulinic acid (10 g, 21.90 mmol) in 1,4-dioxane (100 mL) was added triethylamine (9.16 mL, 65.7 mmol) and diphenyl phosphorazidate (7.08 mL, 32.8 mmol). The mixture was heated to reflux. Upon heating, all solids dissolved. After heating the mixture for 26 h, the mixture was cooled to rt and was concentrated under reduced pressure. The residue was diluted with 100 mL of water and was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-15% EtOAc in hexanes gradient and a Thomson 240 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure. A second batch of less-pure product was concentrated and was repurified using a Thomson 240 g column and the same gradient. The fractions containing the expected product were combined with the first -batch to give the title compound as a white solid (7.76 g, 17.10 mmol, 78 % yield). ¹H NMR (400MHz, *chloroform-d*) δ = 4.75 (s, 1H), 4.67 - 4.62 (m, 1H), 3.20 (dt, *J*=11.3, 5.6 Hz, 1H), 2.55 (td, *J*=10.9, 5.9 Hz, 1H), 2.17 - 2.03 (m, 1H), 1.92 - 1.76 (m, 4H), 1.69 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H), 1.74 - 0.66 (m, 20H).

Step 2: Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl

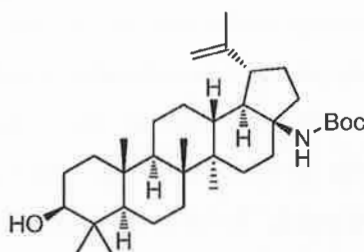


To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (7.76 g, 17.10 mmol) in 1,4-dioxane (100 mL) was added HCl (37%) (21.07 mL, 257 mmol). The mixture was heated to 60 °C for 15 h, then was cooled to rt and concentrated

under reduced pressure. The residue was dissolved in dichloromethane and methanol and was concentrated two additional times to give

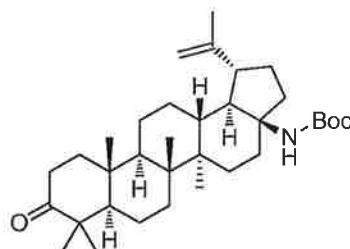
(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl (7.75 g, 16.7 mmol, 98
5 % yield) as an off-white foam. The crude product was used in the next step with no purification.

Step 3: Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate
10



To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol,
15 HCl (7.75 g, 16.7 mmol) in 1,4-dioxane (100 mL) was added water (25 mL), sodium bicarbonate (4.21 g, 50.2 mmol) and Boc anhydride (5.82 mL, 25.08 mmol). The mixture was stirred at rt for 16 h then the mixture was diluted with 100 mL of water and was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced
20 pressure to give tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate as an off-white foam. ¹H NMR (500MHz, *chloroform-d*) δ = 4.74 (d, *J*=1.6 Hz, 1H), 4.64 - 4.62 (m, 1H), 4.34 (br. s., 1H), 3.24 - 3.18 (m, 1H), 2.63 - 2.35 (m, 3H), 2.06 - 1.93 (m, 1H), 1.71 (s, 3H), 1.46 (s, 9H), 1.04 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H),
25 0.86 (s, 3H), 0.79 (s, 3H), 1.77 - 0.68 (m, 22H).

Step 4: Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate

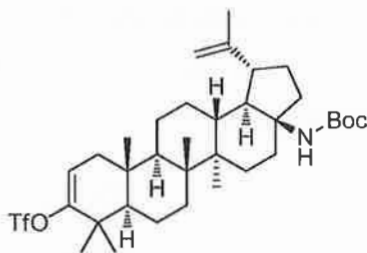


5

To a solution of the resulting tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate in dichloromethane (100 mL) was added pyridinium chlorochromate (4.69 g, 21.74 mmol).

- 10 The mixture was stirred at rt for 5 h then an additional 1.0 g of PCC was added and the mixture was stirred at rt for 1 h. The mixture was filtered through a plug of silica gel and celite which was washed with a solution of 25% ethyl acetate in hexanes. The filtrate was concentrated under reduced pressure to give tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate as a light-yellow foam. ¹H NMR (500MHz, chloroform-d) δ = 4.74 (d, J=1.7 Hz, 1H), 4.63 (t, J=1.7 Hz, 1H), 4.34 (br. s., 1H), 2.65 - 2.34 (m, 5H), 2.05 - 1.88 (m, 2H), 1.71 (s, 3H), 1.47 (s, 9H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 1.76 - 0.93 (m, 18H).

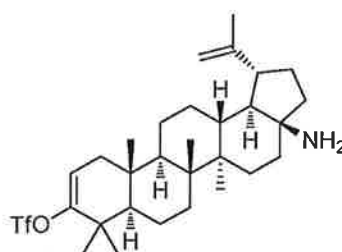
- 20 **Step 5: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate**



- A solution of the resulting tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate in THF (100 mL) was cooled to -78 °C. To the solution was added KHMDS (0.91M in THF) (40.4 mL, 36.8 mmol). The mixture was stirred for 20 minutes at -78 °C then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide (7.47 g, 20.90 mmol) in THF (100 mL) was added via canula. The mixture was stirred at -78 °C for 5 h, then was quenched with 100 mL of water and was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were dried with magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in a small amount of DCM and methanol and the yellow solids that formed were removed by filtration. The filtrate was again concentrated and treated with methanol and the solids that formed were again removed by filtration. The filtrate was concentrated and was adsorbed to silica gel and was then purified by flash chromatography using a 0-50% ethyl acetate in hexanes gradient and a Thomson 240 g silica gel column. The fractions containing the deprotected product were combined and were concentrated under reduced pressure to give a mixture of products. This mixture was repurified by flash chromatography using a 0-10% EtOAc in hexanes gradient and a 240 g Thomson silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give
- (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (1.31 g, 1.99 mmol, 11.9% over 3 steps). ¹H NMR (500MHz, CHLOROFORM-d) δ = 5.57 (dd, J=6.7, 1.8 Hz, 1H), 4.73 (s, 1H), 4.62 (s, 1H), 4.32 (br. s., 1H), 2.64 - 2.31 (m, 3H), 2.16 (dd, J=17.0, 6.8 Hz, 1H),

2.04 - 1.94 (m, 1H), 1.70 (s, 3H), 1.45 (s, 9H), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.86 (m, 18H).

Step 6: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

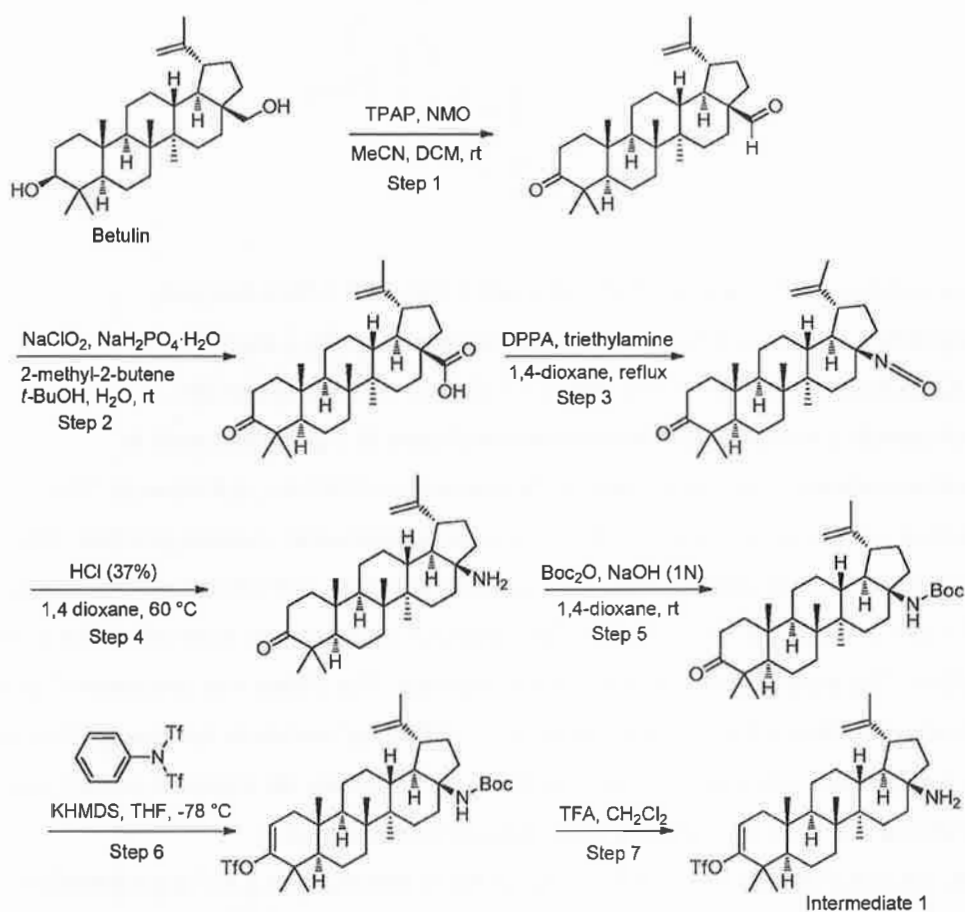


To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.2 g, 0.304 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.5 mL, 6.49 mmol). The mixture was stirred at rt for 1.5 h then was concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated and adsorbed to silica gel and purified using a 12-100% ethyl acetate in hexanes gradient and a 12 g Thomson silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.109 g, 0.195 mmol, 64.3 % yield) as an off-white solid. ¹H NMR (500MHz, *chloroform-d*) δ = 5.57 (dd, *J*=6.8, 1.9 Hz, 1H), 4.73 (d, *J*=1.6 Hz, 1H), 4.63 - 4.60 (m, 1H), 2.54 (td, *J*=10.9, 5.3 Hz, 1H), 2.17 (dd,

$J=17.1, 6.9$ Hz, 1H), 2.08 - 1.99 (m, 1H), 1.70 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.91 (m, 20H).

Method 2: Intermediate 1

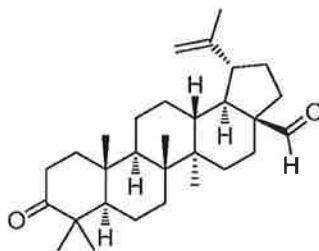
- 5 **Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate**



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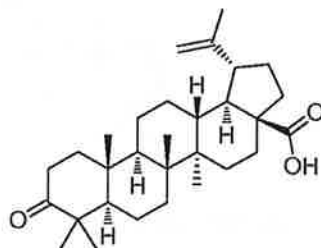
Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carbaldehyde

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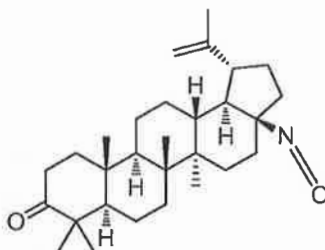
To suspension of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-(hydroxymethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (20 g, 45.2 mmol) in acetonitrile (200 mL) and DCM (300 mL) was added 4 angstrom molecular sieves (5 g) and the mixture was stirred for 10 minutes at rt. To the mixture was then added NMO (15.88 g, 136 mmol) and TPAP (0.794 g, 2.259 mmol). The dark green mixture was stirred under nitrogen overnight. Additional NMO (2.0 g) and TPAP (0.08 g) were added and the mixture was stirred at rt for 7 h. The mixture was filtered through a pad of silica gel and celite which was washed with dichloromethane then 25% EtOAc in hexanes. The filtrate was concentrated under reduced pressure and purified using a Thomson 240 g silica gel column and a 15-20% ethyl acetate in hexanes gradient. The title product was isolated as a white foam (17.6g, 40.1 mmol, 89%). ¹H NMR (400MHz, chloroform-d) δ = 9.68 (d, J =1.5 Hz, 1H), 4.77 (d, J =2.0 Hz, 1H), 4.66 - 4.63 (m, 1H), 2.89 (td, J =11.2, 5.8 Hz, 1H), 2.56 - 2.36 (m, 2H), 2.16 - 2.03 (m, 2H), 1.97 - 1.84 (m, 2H), 1.71 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 1.83 - 0.87 (m, 18H).

Step 2: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid



To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carbaldehyde (17.6 g, 36.1 mmol) in t-BuOH (100 mL) was added 2-methyl-2-butene (40 mL, 476 mmol). A solution of sodium chlorite (15 g, 133 mmol) and sodium phosphate monobasic monohydrate (25 g, 181 mmol) in water (200 mL) was added drop wise over 1.25 h and the mixture was stirred at rt for an additional 45 minutes. The mixture was diluted with saturated aqueous ammonium chloride (100 mL) and extracted with ethyl acetate (3 x 125 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by using a 300g Thomson silica gel column and a 10-50% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid as a white foam (16.4g, 36.1 mmol, 100%). LCMS: m/e 453.2 (M-H)⁻, 2.61 min (method 3). ¹H NMR (400MHz, chloroform-d) δ = 10.02 (br. s., 1H), 4.75 (d, J=1.8 Hz, 1H), 4.64 - 4.61 (m, 1H), 3.02 (td, J=10.8, 4.8 Hz, 1H), 2.55 - 2.36 (m, 3H), 2.33 - 2.19 (m, 2H), 2.08 - 1.86 (m, 4H), 1.70 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 1.82 - 0.90 (m, 15H).

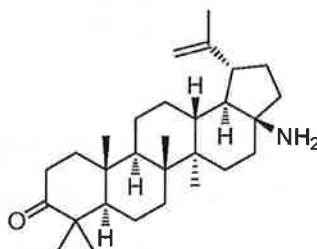
Step 3: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one



To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-

carboxylic acid (16.41 g, 36.1 mmol) in 1,4-dioxane (200 mL) was added triethylamine (15.09 mL, 108 mmol) and diphenyl phosphorazidate (11.67 mL, 54.2 mmol). The mixture was heated to reflux for 18.5 h, then was cooled to rt and concentrated under reduced pressure. The residue was split into two portions and was purified using a 0-15% ethyl acetate in hexanes gradient and a Thomson 240g silica gel column to purify each portion. The fractions containing the expected product were combined and concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (10.3 g, 22.80 mmol, 63.2 % yield) as an off-white foam. ¹H NMR (400MHz, chloroform-d) δ = 4.75 (d, J =2.0 Hz, 1H), 4.66 - 4.63 (m, 1H), 2.60 - 2.36 (m, 4H), 2.17 - 2.04 (m, 1H), 1.69 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 0.95 (s, 6H), 2.01 - 0.71 (m, 20H).

Step 4: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one, HCl



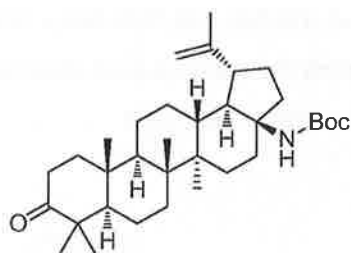
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To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (10.3 g, 22.80 mmol) in 1,4-dioxane (100 mL) was added HCl (37%) (28.1 mL, 342 mmol). The mixture was heated to 60 °C for 15.5h then was cooled to rt and was concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate (150 mL) and was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using a 20-60% ethyl acetate in hexanes gradient with 0.1% triethyl amine added to the mixture. The

fractions containing the expected product were combined and concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one, HCl (5.4 g, 11.68 mmol, 51.2 % yield) as a yellow foam. LCMS: m/e 426.5 (M+H)⁺,

- 5 1.59 min (method 1). ¹H NMR (400MHz, CHLOROFORM-d) δ = 4.73 (d, J =2.3 Hz, 1H), 4.60 (dd, J =2.4, 1.4 Hz, 1H), 2.58 - 2.37 (m, 3H), 2.11 - 1.98 (m, 1H), 1.94 - 1.87 (m, 1H), 1.69 (d, J =0.5 Hz, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 1.79 - 0.91 (m, 20H).

- 10 **Step 5: Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate**



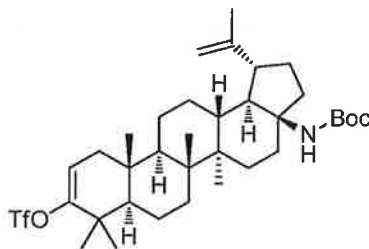
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To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (5.25 g, 12.33 mmol) in 1,4-dioxane (50 mL) was added sodium hydroxide (1N) (24.67 mL, 24.67 mmol) followed by di-tert-butyl dicarbonate (3.15 mL, 13.57 mmol). The mixture was stirred at rt for 2 h then 30 mL of methanol, 50 mL of dichloromethane and 20 mL of water were added to help solubilize the mixture. After stirring for 1.5 h at rt, the reaction was not complete, so di-tert-butyl dicarbonate (0.3 g) was added and the mixture stirred at rt for 3 h. Again di-tert-butyl dicarbonate (0.3 g) was added and the mixture was stirred at rt for 16 h. Since traces of starting material were still present, di-tert-butyl dicarbonate (1 g) was added to the mixture and the stirring was continued for 6 h at which point TLC showed no starting material remaining. The mixture was diluted with water (75 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with water (100 mL) then were dried with sodium sulfate,

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filtered and concentrated under reduced pressure. The residue was purified using a 0-10% ethyl acetate in hexanes gradient and a 240 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate (5.85 g, 11.13 mmol, 90 % yield) as a white foam. ¹H NMR (400MHz, chloroform-d) δ = 4.72 (s, 1H), 4.62 (s, 1H), 4.33 (br. s., 1H), 2.64 - 2.32 (m, 5H), 2.06 - 1.84 (m, 2H), 1.69 (s, 3H), 1.45 (s, 9H), 1.08 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 1.74 - 0.86 (m, 18H).

Step 6: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate



A flask containing a solution of tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate (1.2 g, 2.282 mmol) and 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide (1.019 g, 2.85 mmol) in THF (20 mL) was cooled to -78 °C. To the solution was added KHMDS (0.91 M in THF) (5.52 mL, 5.02 mmol). The mixture was stirred at -78 °C for 1 h then warmed to rt and stirred for 1 h. The reaction was then quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The crude material was purified using a 0-12% ethyl acetate in hexanes gradient and a Thomson 80

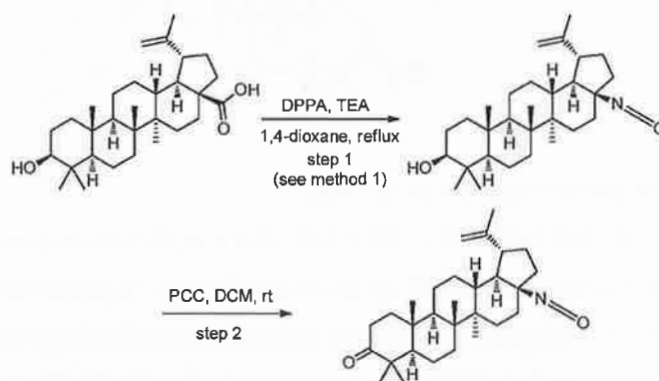
g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give

(1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.9 g, 1.368 mmol, 59.9 % yield) as a white foam. ¹H NMR (500MHz, chloroform-d) δ = 5.57 (dd, J =6.7, 1.8 Hz, 1H), 4.73 (s, 1H), 4.62 (s, 1H), 4.32 (br. s., 1H), 2.64 - 2.31 (m, 3H), 2.16 (dd, J =17.0, 6.8 Hz, 1H), 2.04 - 1.94 (m, 1H), 1.70 (s, 3H), 1.45 (s, 9H), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 10 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.86 (m, 18H).

Step 7: Same experimental procedure described for Step 6 in method 1 above.

- Alternatively, the intermediate (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-15 isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one can be prepared from betulinic acid following the scheme shown below:



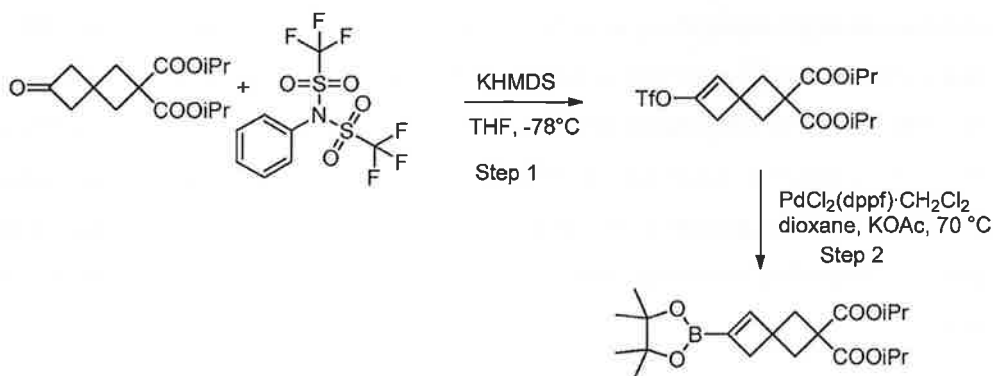
- 20 **Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol.**

The title compound was prepared using the same conditions described above in Step 1, method 1 using betulinic acid as starting material.

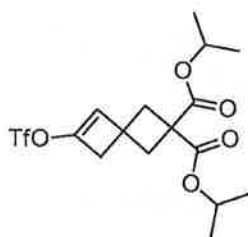
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Step 2: To a solution of 24g of crude (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol in dichloromethane (200 mL) was added PCC (11.80 g, 54.8 mmol) in three portions over 45 minutes. The mixture was stirred at rt for 4h, then an additional 1g of PCC was added and the mixture was further stirred at rt for 2h. The mixture was filtered through a plug of silica gel and celite and the plug was washed with a 1:1 solution of ethyl acetate : hexanes. The filtrate was concentrated under reduced pressure to give the crude product which was used in the next step with no additional purification. ¹H NMR (500MHz, Chloroform-d) δ = 4.76 - 4.74 (m, 1H), 4.65 - 4.63 (m, 1H), 2.62 - 2.36 (m, 3H), 2.16 - 2.03 (m, 1H), 1.69 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 0.96 (s, 6H), 1.95 - 0.91 (m, 21H).

Preparation of diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate

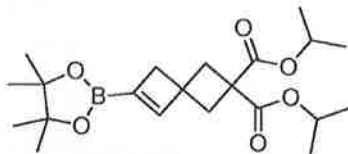


Step 1: Preparation of diisopropyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2,2-dicarboxylate



A solution of diisopropyl 6-oxospiro[3.3]heptane-2,2-dicarboxylate (prepared as described in *Tetrahedron: Asymmetry*. **2008**, *19*, 2924-293) (5.36 g, 18.98 mmol) in THF (40 mL) was cooled to -78 °C. To the solution was added KHMDS (0.91M in THF) (31.3 mL, 28.5 mmol). The mixture was stirred for 30 minutes at -78 °C then a solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (8.48 g, 23.73 mmol) in THF (40 mL) was added via cannula. After 4.5 h of stirring at -78 °C, an additional 2.0 g of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide was added to the mixture and it was further stirred at - 78 °C. After 1 h of stirring, the mixture was diluted with water (100 mL), was warmed to rt and was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash chromatography using a Thomson 240 g silica gel column and a 0-12% ethyl acetate in hexanes gradient. The fractions containing the product were combined and were concentrated under reduced pressure to give diisopropyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2,2-dicarboxylate (1.16 g, 2.80 mmol, 14.74 % yield) as a clear, colorless oil that partially solidified under vacuum at rt. ¹H NMR (500MHz, CHLOROFORM-d) δ = 5.53 (s, 1H), 5.14 - 5.03 (m, 2H), 2.95 (s, 2H), 2.77 (s, 4H), 1.27 (d, *J*=6.3 Hz, 6H), 1.26 (d, *J*=6.3 Hz, 6H). Note: A small amount of impurity was also present in the sample and was visible in the aromatic region of the spectra. The product was used in the next step of the reaction sequence with the impurity present.

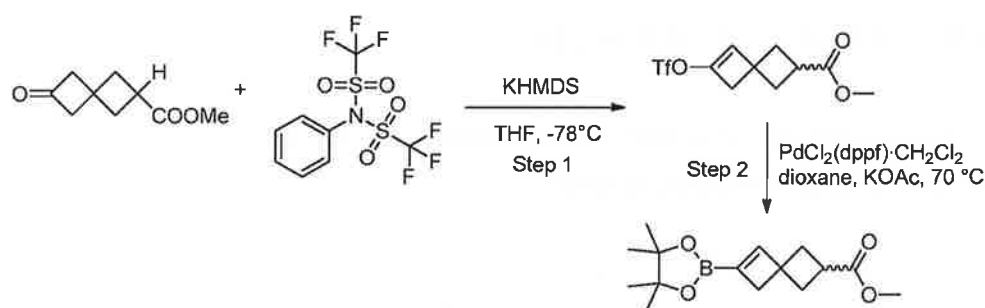
Step 2: Preparation of diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate



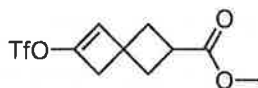
To a rbf containing diisopropyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2,2-dicarboxylate (1.16 g, 2.80 mmol) was added bis(binacolato)diboron (0.782 g, 3.08

mmol), potassium acetate (0.687 g, 7.00 mmol), and $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (0.069 g, 0.084 mmol). The mixture was diluted with dioxane (10 mL), flushed with N_2 , and heated to 70 °C for 22 h. The mixture was cooled to rt, diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-10% ethyl acetate in hexanes gradient and a Thomson 40 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (1.044 g, 2.66 mmol, 95 % yield) as a yellow oil. ^1H NMR (400MHz, Chloroform- d) δ = 6.86 (s, 1H), 5.05 (dd, J =11.8, 6.3 Hz, 2H), 2.70 (s, 4H), 2.61 (s, 2H), 1.26 (s, 12H), 1.23 (d, J =6.3 Hz, 1H), 1.23 (d, J =6.3 Hz, 1H).

Preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate



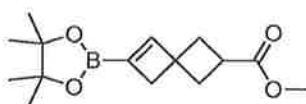
Step 1: Preparation of methyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2-carboxylate



A solution of methyl 6-oxospiro[3.3]heptane-2-carboxylate (prepared as described in *Tetrahedron: Asymmetry*. **2008**, *19*, 2924-2930) (0.599 g, 3.56 mmol) in THF (6 mL)

was cooled to -78 °C. To the solution was added KHMDS (0.91 M in THF) (4.89 mL, 4.45 mmol). The mixture was stirred for 30 minutes at -78 °C then a solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.527 g, 4.27 mmol) in THF (6 mL) was added via cannula. After 4 h of stirring at -78 °C, the reaction was diluted with water (20 mL), warmed to rt and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient and a Thomson 40 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2-carboxylate (0.242 g, 0.806 mmol, 22.6 % yield) as a clear, light-yellow oil. ¹H NMR showed a mixture of the two diastereomers (0.4:1 ratio) which were not separated and were used in the next step with no additional purification. Isomer 1 (minor): ¹H NMR (500MHz, CHLOROFORM-d) δ = 5.58 (s, 1H), 3.71 (s, 3H), 3.14 - 3.05 (m, 1H), 2.90 (s, 2H), 2.60 - 2.52 (m, 2H), 2.47 - 2.40 (m, 2H). Isomer 2 (major): ¹H NMR (500MHz, chloroform-d) δ = 5.48 (s, 1H), 3.70 (s, 3H), 3.14 - 3.05 (m, 1H), 2.94 (s, 2H), 2.60 - 2.52 (m, 2H), 2.47 - 2.40 (m, 2H).

Step 2: Preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate



To a vial containing methyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2-carboxylate (0.242 g, 0.806 mmol) (0.4:1 mixture of diastereomers) was added bis(binacolato)diboron (0.225 g, 0.887 mmol), potassium acetate (0.198 g, 2.015 mmol), and PdCl₂(dppf)-CH₂Cl₂ Adduct (0.020 g, 0.024 mmol). The mixture was diluted with 1,4-dioxane (5 mL), flushed with nitrogen and the vial was sealed and heated to 70 °C for 23 h. The mixture was cooled to rt and filtered through a plug of silica gel and celite (washed with 25% EtOAc in hexanes). The filtrate was concentrated under reduced pressure to give methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-

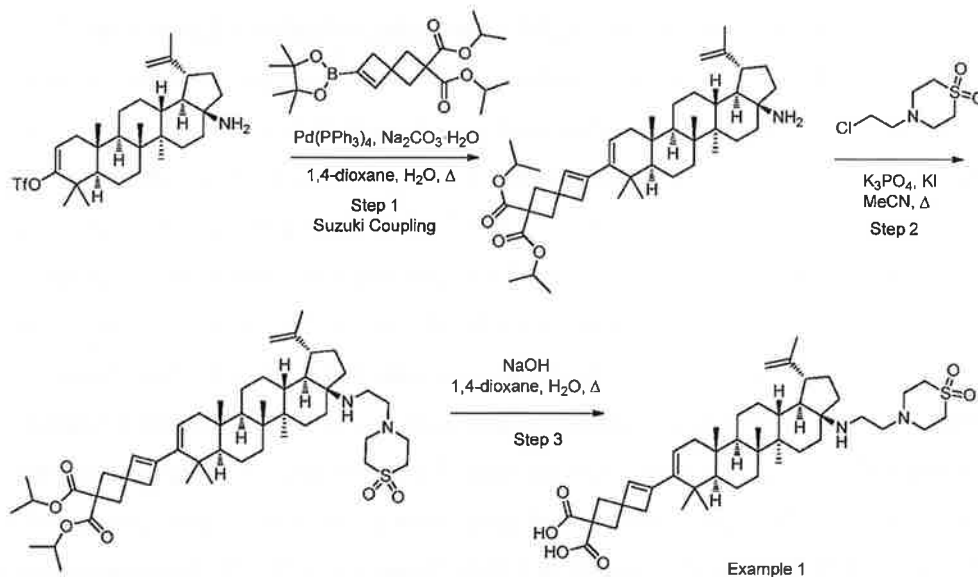
ene-2-carboxylate (0.224 g, 0.806 mmol, 100 % yield) as a brown oil. ¹H NMR showed a mixture of the two diastereomers (0.8:1 ratio) which were not separated, but were used in the next step with no additional purification. Isomer 1 (minor): ¹H NMR (500MHz, CHLOROFORM-d) δ = 7.02 (s, 1H), 3.68 (s, 3H), 3.05 (dq, *J*=17.6, 8.7 Hz, 1H), 2.55 (s, 2H), 2.53 - 2.46 (m, 2H), 2.41 - 2.32 (m, 2H), 1.29 - 1.26 (m, 12H). Isomer 2 (major): ¹H NMR (500MHz, CHLOROFORM-d) δ = 6.81 (s, 1H), 3.68 (s, 3H), 3.05 (dq, *J*=17.6, 8.7 Hz, 1H), 2.66 (s, 2H), 2.53 - 2.46 (m, 2H), 2.41 - 2.32 (m, 2H), 1.28 - 1.26 (m, 12H). (Note: excess bis(binacolato)diboron is also seen in the multiplet at 1.29-1.26 ppm and will be removed after the subsequent step).

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Example 1

Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid, HCl

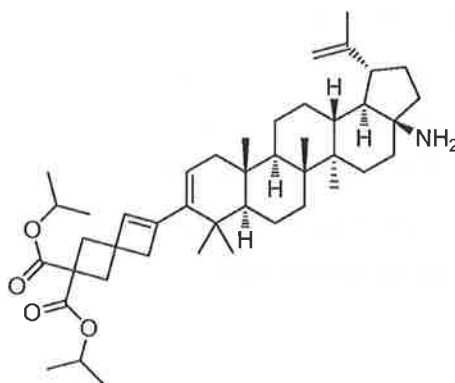
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Step 1: Suzuki coupling- Preparation of diisopropyl 6-

20 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate



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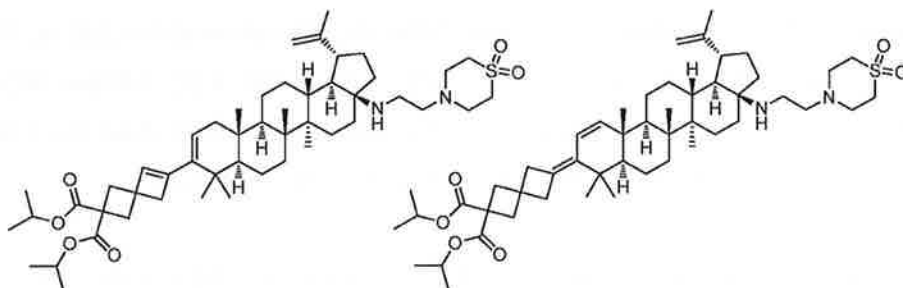
To a vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (1.54 g, 2.76 mmol) was added diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (1.044 g, 2.66 mmol), sodium carbonate monohydrate (0.856 g, 6.90 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.096 g, 0.083 mmol). The mixture was diluted with 1,4-dioxane (12 mL) and water (3 mL), then was flushed with nitrogen and the vial was sealed and heated to 85 °C. After 5.5 h of heating, the mixture was cooled to rt. The mixture was diluted with water (40 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-50% ethyl acetate in hexanes gradient and a Thomson 80g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (1.19 g, 1.766 mmol, 63.9 % yield) as an off-white solid. LCMS: m/e 674.7 (M+H)⁺, 2.30 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 5.87 (s, 1H), 5.52 (dd, J=6.4, 1.8 Hz, 1H), 5.13 - 5.01 (m, 2H), 4.73 (br. s., 1H), 4.61 (br. s., 1H), 2.74 - 2.66 (m, 4H), 2.63 - 2.51 (m, 3H), 2.14

- 1.99 (m, 2H), 1.70 (s, 3H), 1.27 - 1.23 (m, 12H), 1.15 (s, 3H), 1.07 (br. s., 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H), 1.76 - 0.80 (m, 20H).

Step 2: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate

and

diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,6,7,7a,8,11b,12,13,13a-tetradecahydro-1H-cyclopenta[a]chrysen-9(5bH,11aH,13bH)-ylidene)spiro[3.3]heptane-2,2-dicarboxylate



To a sealable flask was added diisopropyl 6-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.05 g, 0.074 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.052 g, 0.223 mmol), potassium iodide (0.032 g, 0.193 mmol) and phosphoric acid, potassium salt (0.079 g, 0.371 mmol). The mixture was diluted with acetonitrile (1 mL), flushed with nitrogen, sealed and heated to 120 °C for 18.5 h. The mixture was cooled to rt, concentrated under reduced pressure and purified using a 0-50% ethyl acetate in hexanes gradient and a Thomson 12g silica gel column. The fractions containing the products were combined and concentrated

under reduced pressure to give 24 mg of a mixture of two compounds as an off-white foam. The two compounds were separated by supercritical fluid chromatography to give two regioisomeric products: The diisopropyl 6-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (6.6 mg, 0.0079 mmol, 10.7% yield) and diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11b,12,13,13a-tetradecahydro-1H-cyclopenta[a]chrysen-9(5bH,11aH,13bH)-ylidene)spiro[3.3]heptane-2,2-dicarboxylate (9.1 mg, 0.0109 mmol, 14.7% yield). For diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate LCMS: m/e 835.7 (M+H)⁺, 2.24 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 5.87 (s, 1H), 5.54 - 5.49 (m, 1H), 5.13 - 5.01 (m, 2H), 4.72 (s, 1H), 4.60 (s, 1H), 3.12 - 2.99 (m, 9H), 2.75 - 2.43 (m, 12H), 2.10 (dd, J=17.9, 6.5 Hz, 1H), 1.69 (s, 3H), 1.25 (t, J=6.1 Hz, 12H), 1.15 (s, 3H), 1.07 (s, 6H), 0.97 (s, 3H), 0.82 (s, 3H), 2.02 - 0.77 (m, 20H).

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For diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11b,12,13,13a-tetradecahydro-1H-cyclopenta[a]chrysen-9(5bH,11aH,13bH)-ylidene)spiro[3.3]heptane-2,2-dicarboxylate LCMS: m/e 835.7

(M+H)⁺, 2.23 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 5.87 (d, J=10.1 Hz, 1H), 5.73 (d, J=9.9 Hz, 1H), 5.10 - 5.01 (m, 2H), 4.72 (s, 1H), 4.61 (s, 1H), 3.13 - 2.94 (m, 10H), 2.87 - 2.73 (m, 2H), 2.71 - 2.43 (m, 9H), 1.69 (s, 3H), 1.24 (dd, J=6.2, 2.4 Hz, 12H), 1.10 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 2.01 - 0.80 (m, 21H).

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Step 3: To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

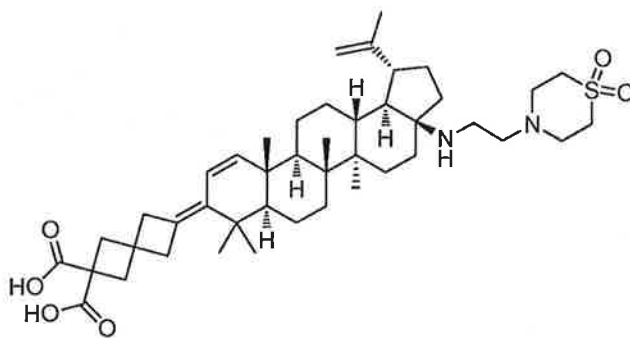
cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (6.6 mg, 7.90 μmol) in 1,4-dioxane (1 mL) was added NaOH (10N) (0.05 mL, 0.500 mmol) and the mixture was heated to 85 °C for 23.25 h. The mixture was cooled to rt then was diluted with 1,4-dioxane (0.5 mL) and methanol (1 mL). The mixture was then acidified by adding 1N HCl and further diluted with water (2 mL). The solids formed were collected by filtration to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid, HCl (4.0 mg, 5.0 μmol , 63 % yield) as a white solid. LCMS: m/e 751.6 ($M+H$)⁺, 1.62 min (method 1). ¹H NMR (500MHz, acetic acid-d₄,) δ = 5.98 (s, 1H), 5.61 (d, $J=4.4$ Hz, 1H), 4.83 (s, 1H), 4.73 (s, 1H), 3.45 (d, $J=11.8$ Hz, 1H), 3.34 - 3.01 (m, 12H), 2.98 - 2.91 (m, 1H), 2.84 (s, 4H), 2.71 - 2.63 (m, 2H), 1.77 - 1.74 (m, 3H), 1.27 - 1.25 (m, 3H), 1.21 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.93 (s, 3H), 2.32 - 0.87 (m, 21H).

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Example 2

Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11b,12,13,13a-tetradecahydro-1H-cyclopenta[a]chrysen-9(5bH,11aH,13bH)-ylidene)spiro[3.3]heptane-2,2-dicarboxylic acid, HCl

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To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11b,12,13,13a-tetradecahydro-1H-cyclopenta[a]chrysen-

25

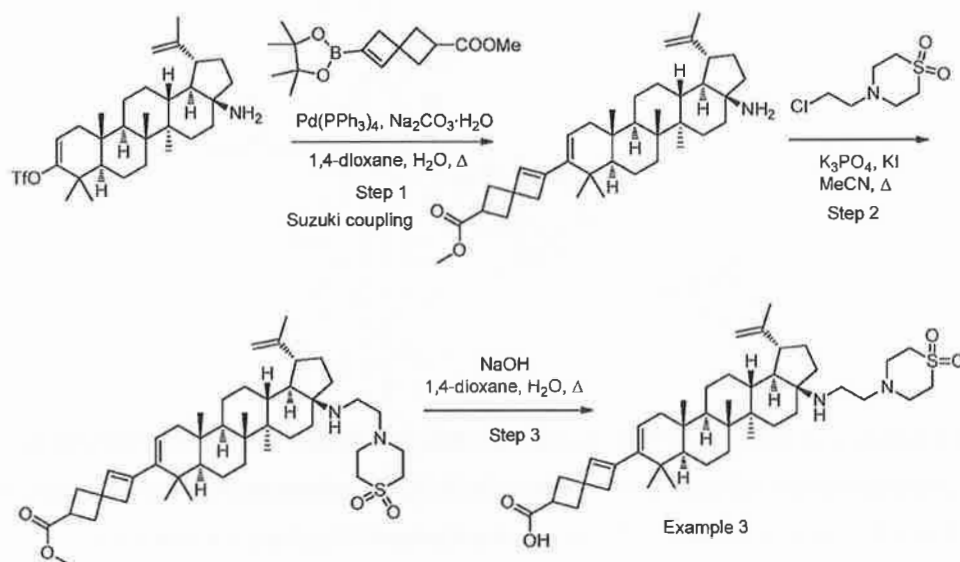
9(5bH,11aH,13bH)-ylidene)spiro[3.3]heptane-2,2-dicarboxylate (9.1 mg, 10.90 μmol) in 1,4-dioxane (1 mL) was added NaOH (10N) (0.05 mL, 0.500 mmol) and the mixture was heated to 85 °C. After 23.25 h of heating, the mixture was cooled to rt then diluted with 1,4-dioxane(0.5 mL) and methanol(1 mL). The mixture was acidified by adding 1N HCl and further diluted with water (2 mL). The solids formed were collected by filtration to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,6,7,7a,8,11b,12,13,13a-tetradecahydro-1H-cyclopenta[a]chrysen-9(5bH,11aH,13bH)-ylidene)spiro[3.3]heptane-2,2-dicarboxylic acid, HCl (6 mg, 7.6 μmol , 70 % yield) as a white solid. LCMS: m/e 751.6 ($M+H$)⁺, 1.98 min (method 1). ¹H NMR (500MHz, acetic acid- d_4) δ = 5.92 (d, $J=9.9$ Hz, 1H), 5.81 (d, $J=9.8$ Hz, 1H), 4.84 (br. s., 1H), 4.74 (s, 1H), 3.45 (br. s., 1H), 3.36 - 3.00 (m, 13H), 2.98 - 2.79 (m, 3H), 2.74 (d, $J=7.7$ Hz, 4H), 1.76 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 2.32 - 0.87 (m, 20H).

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Example 3

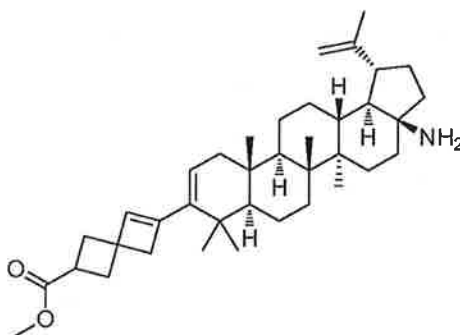
Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylic acid, HCl

20



Step 1: Suzuki coupling -Preparation of methyl 6-

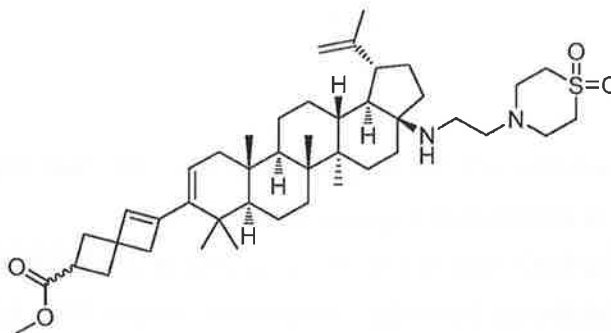
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylate



To a vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.418 g, 0.749 mmol) was added methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate (0.250 g, 0.899 mmol), sodium carbonate monohydrate (0.232 g, 1.874 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.026 g, 0.022 mmol). The mixture was diluted with 1,4-dioxane (4 mL) and water (1 mL), then was flushed with nitrogen and the vial was sealed and heated to 85 °C. After 5.5 h of heating, the mixture was cooled to rt, concentrated under reduced pressure, adsorbed to silica gel, and purified by chromatography using a 0-45% ethyl acetate in hexanes gradient and a 40 g Thomson silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylate (0.31 g, 0.554 mmol, 73.9 % yield) as an off-white solid. ¹H NMR showed a mixture of the two diastereomers (0.8:1 ratio) which were not separated and were used in the next step with no additional purification. LCMS: m/e 560.47 (M+H)⁺, 2.46 min (method 2). Mixture of

diastereomers: ^1H NMR (500MHz, chloroform-d) δ = 6.00 (s, 0.45H, minor diastereomer), 5.84 (s, 0.55H, major diastereomer), 5.54 (td, J =6.1, 2.2 Hz, 1H), 4.75 (d, J =2.0 Hz, 1H), 4.62 (dd, J =2.3, 1.3 Hz, 1H), 3.71 (m, 3H), 3.13 - 2.99 (m, 1H), 2.70 - 2.31 (m, 7H), 2.18 - 1.84 (m, 4H), 1.72 (s, 3H), 1.18 (d, J =3.5 Hz, 3H), 1.10 - 1.08 (m, 6H), 0.99 (s, 3H), 0.85 (s, 3H), 1.68 - 0.83 (m, 19H).

Step 2: Preparation of methyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylate



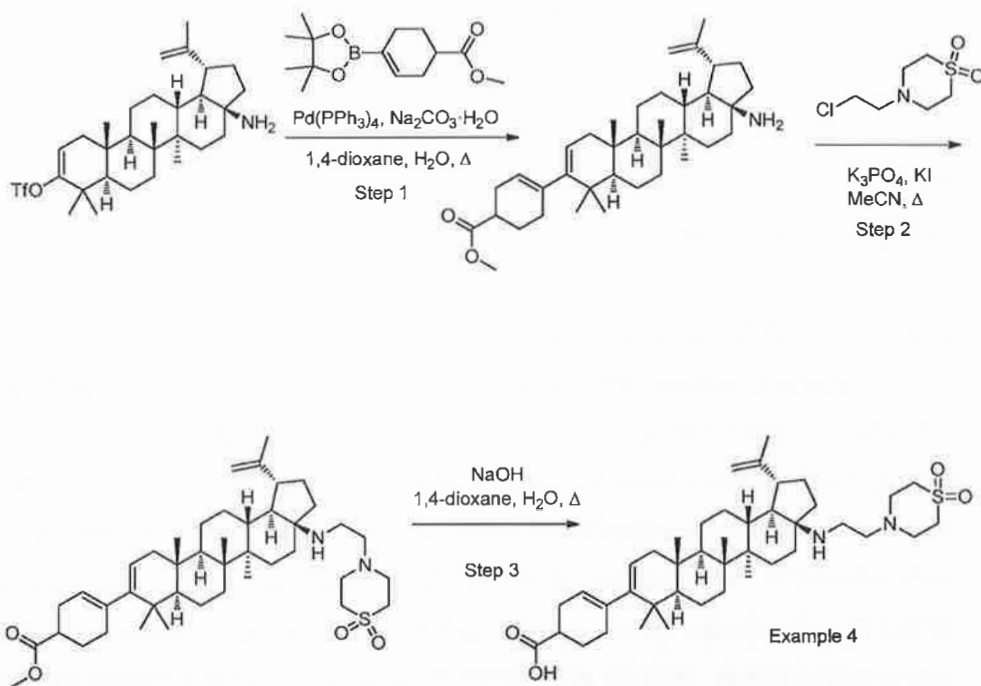
To a scalable vial was added methyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylate (0.25 g, 0.447 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.25 g, 1.068 mmol), potassium iodide (0.222 g, 1.340 mmol) and phosphoric acid, potassium salt (0.474 g, 2.233 mmol). The mixture was diluted with acetonitrile (4 mL), was flushed with nitrogen, then was sealed and heated to 100 °C for 15.5 h. The mixture was cooled to rt, diluted with water (30 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography using a 40 g Thomson silica gel column and a 6-50% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-

dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylate (0.20 g, 0.277 mmol, 62.1
% yield) as an off-white foam. ¹H NMR showed a mixture of the two diastereomers
5 (0.8:1 ratio) which were not separated and were used in the next step with no additional
purification. LCMS: m/e 721.7 (M+H)⁺, 2.04 min (method 1).

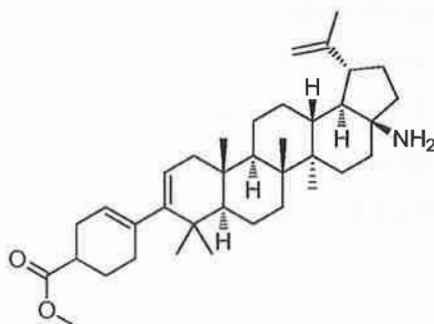
Step 3: To a solution of methyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
10 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylate (0.025 g, 0.035 mmol) in
1,4-dioxane (2 mL) was added NaOH (10N) (0.2 mL, 2.000 mmol). The mixture was
warmed to 65 °C for 15 h then cooled to rt. The mixture was acidified adding a solution
of HCl (0.2 mL of conc. HCl in 2 mL of water). Water was slowly added to this solution
15 until it turned cloudy. Then the mixture was set aside and solids precipitated out of the
solution. The solids were collected by filtration and washed with water first and then
with diethyl ether to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
20 cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2-carboxylic acid, HCl (22.8 mg, 0.031
mmol, 89 % yield) as an off-white solid. ¹H NMR showed a mixture of diastereomers in
a 0.8:1 ratio. LCMS: m/e 707.7 (M+H)⁺, 1.90 min (method 1). Mixture of
diastereomers: ¹H NMR (500MHz, acetic acid-d₄) δ = 6.08 (s, 0.45H), 5.90 (s, 0.55H),
5.63 - 5.56 (m, 1H), 4.89 (s, 1H), 4.74 (s, 1H), 3.53 - 3.08 (m, 16H), 2.72 - 2.34 (m, 7H),
25 1.76 (s, 3H), 1.28 (s, 3H), 1.22 (d, J=4.6 Hz, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 0.92 (s, 3H),
2.24 - 0.87 (m, 17H).

Example 4

30 **Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA**



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate



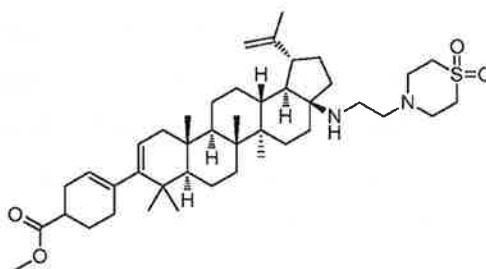
10

To a sealable vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.109 g, 0.195 mmol) was added methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.078

15

g, 0.293 mmol), sodium carbonate hydrate (0.073 g, 0.586 mmol), and tetrakis(triphenylphosphine)palladium(0) (6.77 mg, 5.86 μ mol). The mixture was diluted with 1,4-dioxane (2 mL) and water (0.5 mL) then was flushed with nitrogen, sealed and heated to 85 °C in an oil bath. After 20.5 h, the mixture was cooled to rt, diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and purified by chromatography using a 12g Thomson silica gel column and a 10%-80% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.035 g, 0.064 mmol, 32.7 % yield) as an off-white solid. ¹H NMR (400MHz, chloroform-d) δ = 5.35 (br. s., 1H), 5.19 (d, J =5.8 Hz, 1H), 4.73 (s, 1H), 4.60 (br. s., 1H), 3.69 (s, 3H), 2.55 (td, J =10.7, 5.1 Hz, 2H), 2.31 (d, J =2.3 Hz, 2H), 2.22 - 1.94 (m, 6H), 1.70 (s, 3H), 1.07 (s, 3H), 1.79 - 0.81 (m, 34H).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate



25

To a sealable vial was added methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

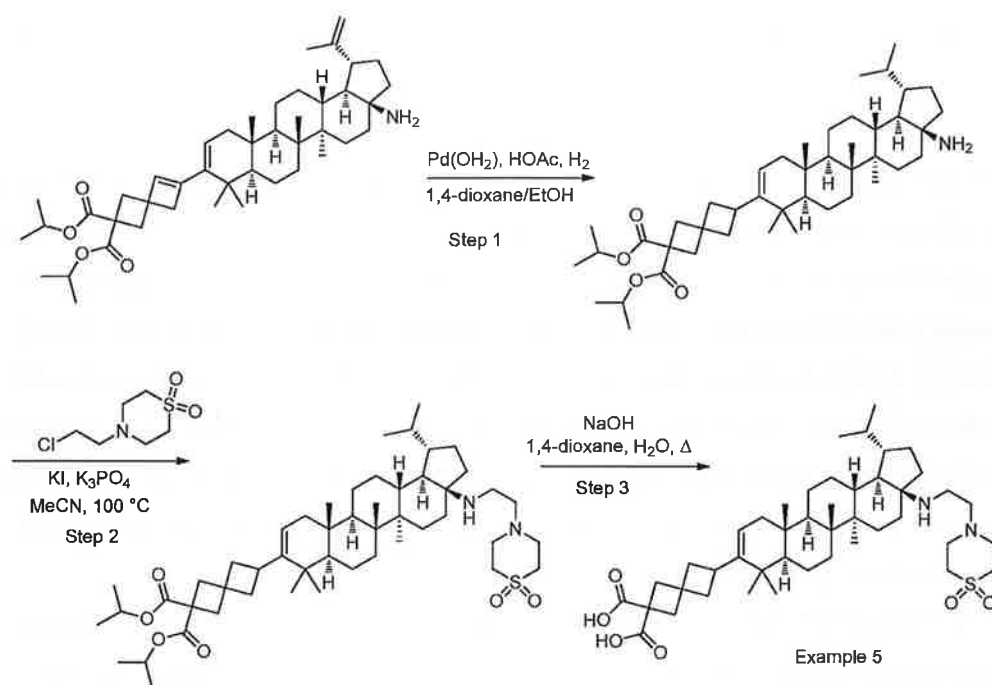
cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.035 g, 0.064 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.045 g, 0.192 mmol), potassium iodide (0.032 g, 0.192 mmol) and phosphoric acid, potassium salt (0.068 g, 0.319 mmol). The mixture was diluted with acetonitrile (1 mL), flushed with nitrogen, sealed and heated to 110 °C. After 21.75h of heating, the mixture was cooled to rt. The crude mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and purified by chromatography using 12 g Thomson silica gel column and a 10-80% EtOAc in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.0295g, 0.042 mmol, 65.1% yield) as a clear film. LCMS: m/e 709.7 (M+H)⁺, 1.90 min (method 1).

Step 3: To a solution of methyl 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.029 g, 0.041 mmol) in 1,4-dioxane (2 mL) was added sodium hydroxide (1N) (0.204 mL, 0.204 mmol). The mixture was warmed to 70 °C. After heating the mixture for 16 h, it was cooled to rt and was acidified by adding 1 mL of 1N HCl. Then water was added until solids formed. The solids were collected by filtration, dissolved in 1,4-dioxane and methanol and purified by prep HPLC (method 2, retention time: 6.6 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (0.014g, 0.02 mmol, 41 % yield) as a white solid. LCMS: m/e 695.6 (M+H)⁺, 1.75 min (method 1). ¹H NMR (400MHz, acetic acid, d₄) δ = 5.37 (br. s., 1H), 5.22 (d, J=6.0 Hz, 1H), 4.80 (s, 1H), 4.70

(s, 1H), 3.50 - 3.42 (m, 1H), 3.32 - 3.03 (m, 11H), 2.93 - 2.84 (m, 1H), 2.63 - 2.54 (m, 1H), 1.72 (s, 3H), 1.22 (s, 3H), 1.08 (s, 3H), 1.02 - 0.92 (m, 9H), 2.37 - 0.79 (m, 28H).

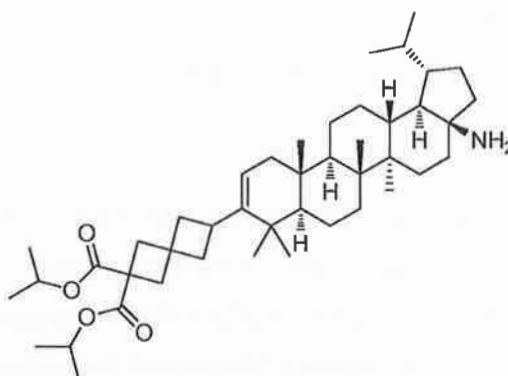
Example 5

- 5 **Preparation of 6-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylic acid, TFA**



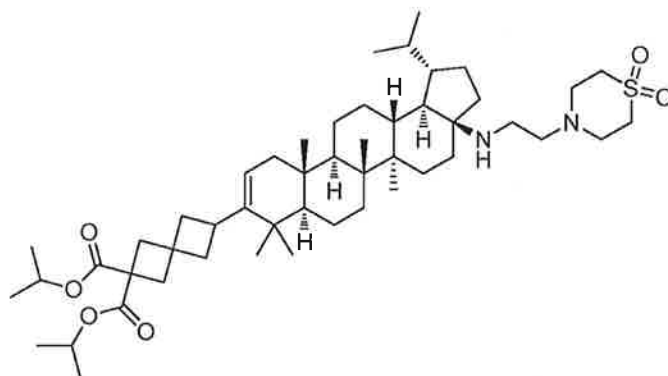
10

- 15 **Step 1. Preparation of diisopropyl 6-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylate**



To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.057 g, 0.085 mmol) in ethanol (2 mL), 1,4-dioxane (2 mL) and acetic acid (0.02 mL, 0.349 mmol) was added palladium hydroxide (20% on carbon) (0.072 g, 0.103 mmol). The mixture as stirred under 1 atm of hydrogen overnight. After stirring the mixture for 15h, it was filtered
 10 through a plug of celite (washed with MeOH) then the filtrate was concentrated under reduced pressure. The residue was diluted with 15 mL of sat. aq. NaHCO₃ and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give diisopropyl 6-
 15 ((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylate (0.057 g, 0.085 mmol, 100 % yield) as an off-white solid. ¹H NMR (500MHz, chloroform-d) δ = 5.33 (d, J=5.7 Hz, 1H), 5.11 - 5.02 (m, 2H), 3.80 - 3.72 (m, 1H), 3.68 - 3.60 (m, 1H), 2.66 (s, 2H), 2.44
 20 (s, 2H), 2.99 - 0.64 (m, 62H).

Step 2. Preparation of diisopropyl 6-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylate
 25



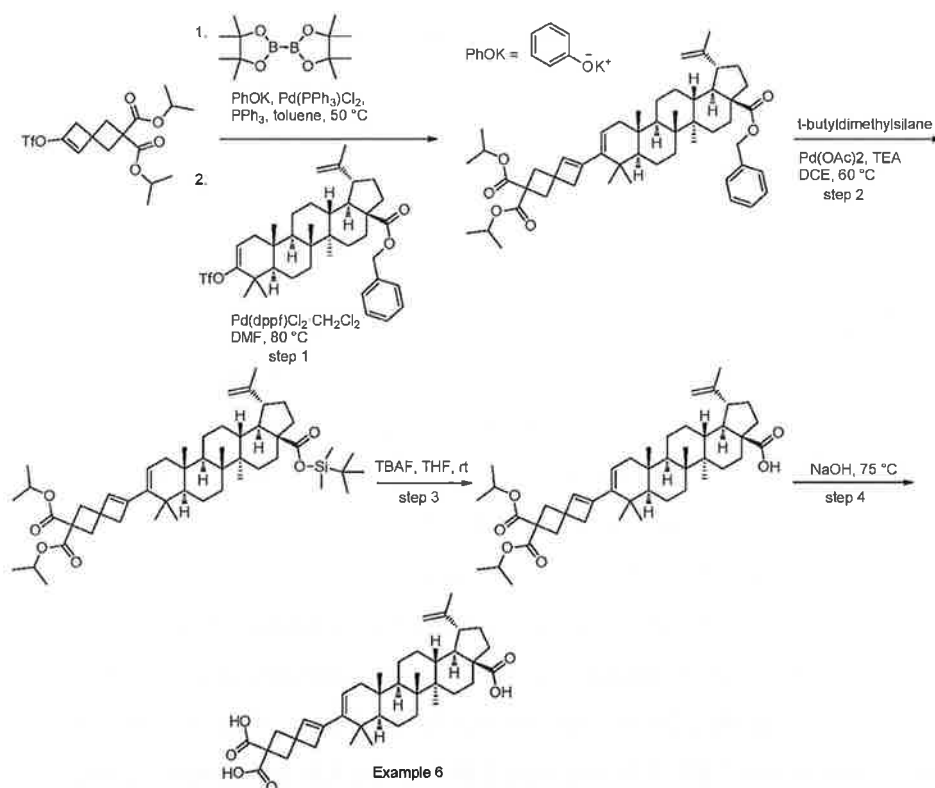
To a sealable vial was added diisopropyl 6-
 ((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-
 5 pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylate (0.057 g, 0.085 mmol), 4-
 (2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.060 g, 0.255 mmol), potassium iodide
 (0.028 g, 0.170 mmol) and phosphoric acid, potassium salt (0.090 g, 0.425 mmol). The
 mixture was diluted with acetonitrile (1.5 mL), flushed with nitrogen, sealed and heated
 10 to 100 °C. After 15 h of heating, the mixture was adsorbed to silica gel and purified by
 flash chromatography using a Thomson 12 g silica gel column and a 12-100% ethyl
 acetate in hexanes gradient. The fractions containing the expected product were
 combined and concentrated under reduced pressure to give diisopropyl 6-
 ((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
 15 dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylate (0.04 g, 0.048 mmol, 56.1
 % yield) as an off-white foam. LCMS: m/e 839.8 (M+H)⁺, 2.33 min (method 1).

20 **Step 3.** To a solution of diisopropyl 6-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylate (0.04 g, 0.048 mmol) in
 1,4-dioxane (2 mL) was added sodium hydroxide (10N) (0.095 mL, 0.953 mmol) and the
 25 mixture was heated to 85 °C. After heating the mixture for 15 h, it was cooled to rt and
 was made acidic by adding 1N HCl. The mixture was then diluted with methanol and

dioxane, filtered through a plug of glass wool and was purified by prep HPLC (method 1, retention time: 5.1 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give 6-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]heptane-2,2-dicarboxylic acid, TFA (0.025g, 0.029 mmol, 60% yield) as an off-white solid. LCMS: m/e 755.6 (M+H)⁺, 1.67 min (method 1). ¹H NMR (400MHz, acetic acid-d₄) δ = 5.38 (d, J=5.8 Hz, 1H), 2.76 (s, 2H), 2.53 (s, 2H), 1.21 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.89 (d, J=6.0 Hz, 6H), 0.81 (d, J=6.5 Hz, 3H), 3.47 - 0.67 (m, 44H).

Example 6

Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid



Step 1: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((benzyloxy)carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

5 **2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate**

The following procedure was modified from *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006.

To a rbf containing diisopropyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.095 g, 0.229 mmol) was added bis(pinacolato)diboron (0.064 g, 0.252 mmol), phenolate, K⁺ (0.045 g, 0.344 mmol), triphenylphosphine (3.61 mg, 0.014 mmol), and bis(triphenylphosphine)palladium(II) chloride (4.83 mg, 6.88 μmol). The mixture was diluted with toluene (2 mL), flushed with nitrogen, then was heated to 50 °C for 3h. The mixture was cooled to rt and TLC showed all starting material had been consumed. To the mixture was added (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(((trifluoromethyl)sulfonyl)oxy)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (0.149 g, 0.220 mmol), phosphoric acid, potassium

salt (0.146 g, 0.688 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (5.62 mg, 6.88 μmol). The mixture was diluted with DMF (2.000 mL), flushed with nitrogen, then was heated to 80 °C. After heating the mixture for an additional 90h, it was cooled to rt and was concentrated under reduced pressure, then was dissolved in DCM and MeOH and was
 5 filtered through a plug of silica gel and celite. The filtrate was concentrated under reduced pressure, and was purified by flash chromatography using a 0-25% ethyl acetate in hexanes gradient and a 12g silica gel column. The major isolate from the purification contained a mixture of products, so it was further purified by flash chromatography using a slower, 0-5, 5-5, 5-10% ethyl acetate/hexanes gradient and a 12g silica gel column. The
 10 fractions containing the expected product were combined and concentrated under reduced pressure to give diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((benzyloxy)carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.053g, 0.047 mmol
 15 (based on 70% purity), 20.4% yield) as a colorless foam. ¹H NMR (500MHz, chloroform-d) δ = 7.40 - 7.30 (m, 5H), 5.86 (s, 1H), 5.51 (dd, J=6.4, 1.8 Hz, 1H), 5.19 - 5.02 (m, 4H), 4.73 (d, J=1.5 Hz, 1H), 4.60 (s, 1H), 3.08 - 2.98 (m, 1H), 2.73 - 2.66 (m, 4H), 2.62 - 2.54 (m, 2H), 1.69 (s, 3H), 2.53 - 0.74 (m, 49H). The material was used in the next step with no additional purification.

20

Step 2: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((tert-butyldimethylsilyl)oxy)carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate.

25 To a rbf containing a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((benzyloxy)carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.053 g, 0.047 mmol (based on 70% purity)) in DCE (2 mL) was added triethylamine
 30 (10.43 μl, 0.075 mmol), *t*-butyldimethylsilane (0.016 mL, 0.094 mmol), and palladium(II) acetate (2.63 mg, 0.012 mmol). The mixture was flushed with nitrogen, then was heated to 60 °C for 4.5h. An additional 3 mg of palladium (II) acetate were added along with 16 μL of *t*-butyldimethylsilane. The mixture was flushed with nitrogen, then was heated to

60 °C for an additional 2.5h. The mixture was cooled to rt and was filtered through a plug of celite and silica gel which was then washed with 25% EtOAc in hexanes. The filtrate was concentrated under reduced pressure to give diisopropyl 6-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((tert-butyl)dimethylsilyl)oxy)carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.026 g, 0.021 mmol (based on 65% purity), 44.2 % yield) as a clear, colorless foam. ¹H NMR (500MHz, chloroform-d) δ = 5.86 (s, 1H), 5.51 (dd, J =6.3, 1.7 Hz, 1H), 5.13 - 5.01 (m, 2H), 4.73 (s, 1H), 4.60 (s, 1H), 3.06 (td, J =10.8, 4.1 Hz, 1H), 2.73 - 2.66 (m, 4H), 2.62 - 2.55 (m, 2H), 1.69 (s, 3H), 0.96 (s, 9H), 2.54 - 0.76 (m, 49H), 0.30 - 0.28 (m, 6H). The material was used in the next step with no additional purification.

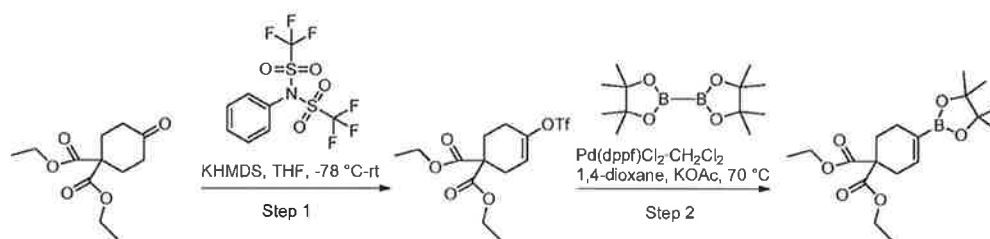
Step 3: Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(6,6-bis(isopropoxycarbonyl)spiro[3.3]hept-1-en-2-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid.

To a solution of diisopropyl 6-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((tert-butyl)dimethylsilyl)oxy)carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (0.026 g, 0.021 mmol (based on 65% purity)) in THF (2 mL) was added TBAF (75% in water) (10.81 mg, 0.031 mmol). The mixture was stirred at rt for 30 minutes, then was diluted with 15 mL of 1N HCl and was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(6,6-bis(isopropoxycarbonyl)spiro[3.3]hept-1-en-2-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (0.024g, 0.021 mmol (based on 60% purity), 100% yield). The material was used in the next step with no additional purification. LCMS: m/e 701.5 (M-H)⁺, 3.35 min (method 3). ¹H NMR (400MHz, chloroform-d) δ = 10.58 (br. s., 1H), 5.87 (s, 1H), 5.52 (d, J =4.8 Hz, 1H), 5.13 - 5.02 (m, 2H), 4.75 (s, 1H),

4.62 (br. s., 1H), 3.07 - 2.97 (m, 1H), 2.70 (s, 4H), 2.63 - 2.55 (m, 2H), 1.70 (s, 3H), 2.54 - 0.77 (m, 49H). The material was used in the next step with no additional purification.

Step 4: To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(6,6-bis(isopropoxycarbonyl)spiro[3.3]hept-1-en-2-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (0.025 g, 0.021 mmol (based on 60% purity)) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.25 mL, 0.250 mmol). The mixture was heated to 75 °C for 66h, then was cooled to rt. LC/MS was inconclusive. To the mixture was added 5 mL of 1N HCl, then the mixture was extracted with dichloromethane (3 x 15 mL) and dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was again dissolved in 1,4-dioxane (3 mL) and 0.1 mL of 10N NaOH was added. The mixture was heated to 75 °C for 16.5h, then was cooled to rt. To the mixture was added 10 mL of 1N HCl then the mixture was further diluted with 10 mL of water and it was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in DMSO and was purified by prep HPLC (method 12, retention time: 10.2 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid (0.015 g, 0.021 mmol (based on 86% purity), 99 % yield) as a white solid. LCMS: m/e 617.4 (M-H)⁻, 2.42 min (method 3). ¹H NMR (500MHz, acetic acid-d₄) δ = 5.93 (s, 1H), 5.58 (d, J=4.6 Hz, 1H), 4.76 (br. s., 1H), 4.62 (br. s., 1H), 3.08 - 2.99 (m, 1H), 2.81 (s, 4H), 2.69 - 2.59 (m, 2H), 1.71 (s, 3H), 2.40 - 0.80 (m, 37H).

Preparation of diethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1,1-dicarboxylate



Step 1: Preparation of diethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1,1-dicarboxylate

- 5 A flask containing a solution of diethyl 4-oxocyclohexane-1,1-dicarboxylate (0.505 g, 2.084 mmol) and 1,1,1-Trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide (0.819 g, 2.293 mmol) in THF (10 mL) was cooled to -78 °C. To the solution was added KHMDS (0.5M in toluene) (6.25 mL, 3.13 mmol). The mixture was stirred at -78 °C for 1.5h then was warmed to rt and was stirred for 1h. The reaction was
- 10 quenched with sat. aq. ammonium chloride (30 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-20% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure
- 15 to give the product which still contained impurities. The residue was repurified using a 0-50% toluene in hexanes gradient followed by a 0-10% ethyl acetate in hexanes. The fractions containing the expected product were combined and concentrated under reduced pressure to give the expected product as a clear, colorless oil (0.417g, 1.114 mmol, 53.4% yield). ¹H NMR (500MHz, chloroform-d) δ = 5.82 - 5.75 (m, 1H), 4.29 - 4.18 (m, 4H),
- 20 2.84 - 2.75 (m, 2H), 2.50 - 2.41 (m, 2H), 2.35 - 2.30 (m, 2H), 1.31 - 1.26 (m, 6H).

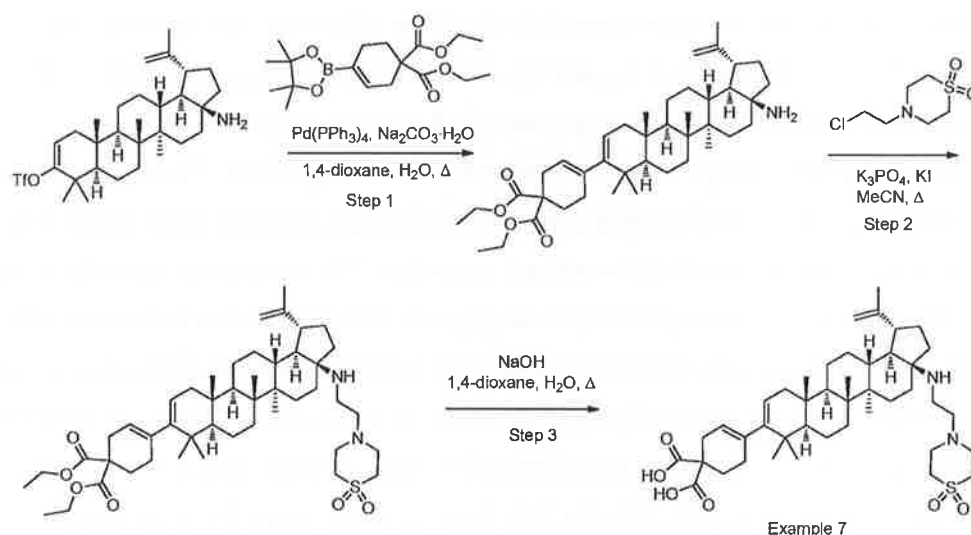
Step 2. Preparation of diethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)sulfonyl)cyclohex-3-ene-1,1-dicarboxylate

- To a flask containing diethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1,1-dicarboxylate (0.4 g, 1.069 mmol) was added bis(pinacolato)diboron (0.285 g, 1.122 mmol), potassium acetate (0.262 g, 2.67 mmol), and 1,1'-
- 25 Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (0.026 g, 0.032 mmol). The mixture was diluted with 1,4-dioxane (10 mL), flushed with nitrogen, and was heated to 70 °C for 5h. The mixture was cooled to rt, diluted with water (25 mL), and extracted

with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 40g silica gel column and a 0-20% ethyl acetate in hexanes gradient. The fractions containing the expected product were
 5 combined and concentrated under reduced pressure to give the title compound as a clear, colorless oil. The product was used in the next step with no additional purification.

Example 7

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylic acid, TFA



Example 7

15

Step 1: Preparation of diethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylate

To a sealable vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.25 g, 0.448 mmol) was added
 20

diethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1,1-dicarboxylate (0.374 g, 0.531 mmol), sodium carbonate hydrate (0.167 g, 1.345 mmol), and palladium tetrakis (0.016 g, 0.013 mmol). The mixture was diluted with 1,4-dioxane (4 mL) and water (1 mL) then was flushed with nitrogen and was sealed and heated to 85 °C in an oil bath. After 5h of heating, the mixture was cooled to rt, was diluted with water (20 mL), and was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 10-50% ethyl acetate in hexanes gradient. diethyl 4-

10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylate, a white solid, was recovered as the minor isolate (0.032g, 0.05 mmol, 11.3% yield). LCMS: m/e 634.6 (M+H)⁺, 2.10 min (method 1).

15

Step 2: Preparation of diethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylate

20 To a sealable vial was added diethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylate (0.032 g, 0.050 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.035 g, 0.151 mmol), potassium iodide (0.025 g, 0.151 mmol), and phosphoric acid, potassium salt (0.078 g, 0.367 mmol). The mixture was diluted with acetonitrile (1 mL), flushed with nitrogen, and was sealed and heated to 100 °C. After 15.5h of heating, the mixture was cooled to rt the mixture was diluted with water (10 mL) and was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate, filtered, and concentrated under

25 reduced pressure. The residue was purified by flash chromatography using a 10-85% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give diethyl 4-

30 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-

dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylate (0.031 g, 0.039 mmol, 77 % yield) as a clear, colorless film. LCMS: m/e 795.7 (M+H)⁺, 2.21 min (method 1).

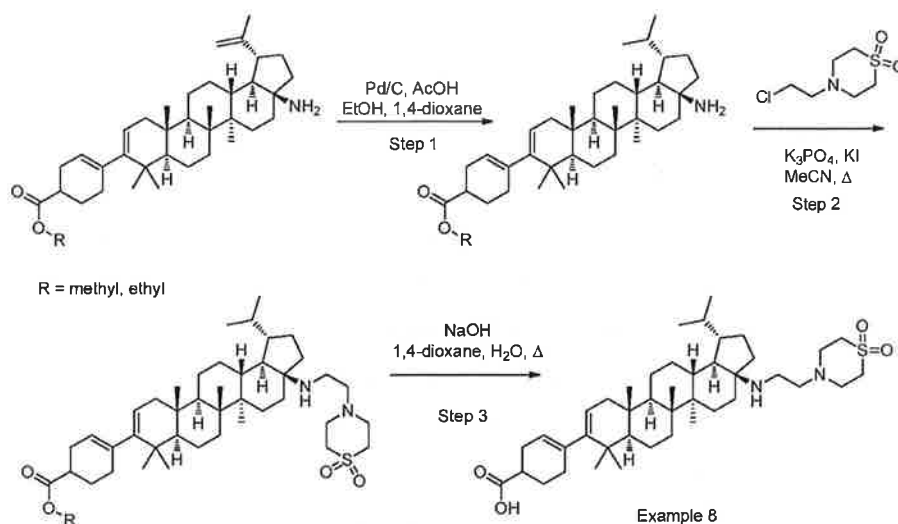
5

Step 3: To a solution of diethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylate (0.031 g, 0.039 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.312 mL, 0.312 mmol). The mixture was heated to 70 °C for 23h, then was cooled to rt. LC/MS showed mono-hydrolyzed product present so NaOH (10N) (0.05 mL, 0.500 mmol) was added and the mixture was heated to 70 °C for an additional 18.5h. The mixture was cooled to rt, diluted with methanol, dioxane, and water, then was purified by prep HPLC (method 3, retention time: 4.8 minutes). The fractions containing the expected product were combined and were concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-ene-1,1-dicarboxylic acid, TFA (12.4 mg, 0.014 mmol, 35 % yield) as a white solid. LCMS: m/e 739.6 (M+H)⁺, 1.50 min (method 1). ¹H NMR (400MHz, acetic acid, d₄) δ = 5.37 (br. s., 1H), 5.20 (d, J=5.3 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.47 (d, J=12.3 Hz, 1H), 3.32 - 3.01 (m, 11H), 2.86 (br. s., 1H), 2.64 (br. s., 2H), 1.71 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.93 (br. s., 3H), 2.29 - 0.87 (m, 26H).

25

Example 8

Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



Step 1: Preparation of ethyl 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a solution of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.1 g, 0.178 mmol) in ethanol (5 mL), 1,4-dioxane (2 mL) and acetic acid (0.051 mL, 0.890 mmol) was added 10% palladium on carbon (0.095 g, 0.089 mmol). The mixture was evacuated and refilled with nitrogen three times then was stirred under 1 atmosphere of hydrogen gas for 16h. The mixture was evacuated and flushed with nitrogen, then was filtered through celite and was concentrated under reduced pressure to give the expected product (0.100g, 0.178 mmol, 100% yield) as an off-white solid. ¹H NMR (400MHz, chloroform-d) δ = 5.36 (br. s., 1H), 5.19 (d, J =5.8 Hz, 1H), 4.19 - 4.11 (m, 2H), 2.57 - 2.47 (m, 1H), 2.31 (dd, J =2.9, 2.1 Hz, 2H), 2.17 (dd, J =4.6, 2.6 Hz, 2H), 2.12 - 0.70 (m, 52H).

Step 2: Preparation of ethyl 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a sealable vial was added ethyl 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethyl-

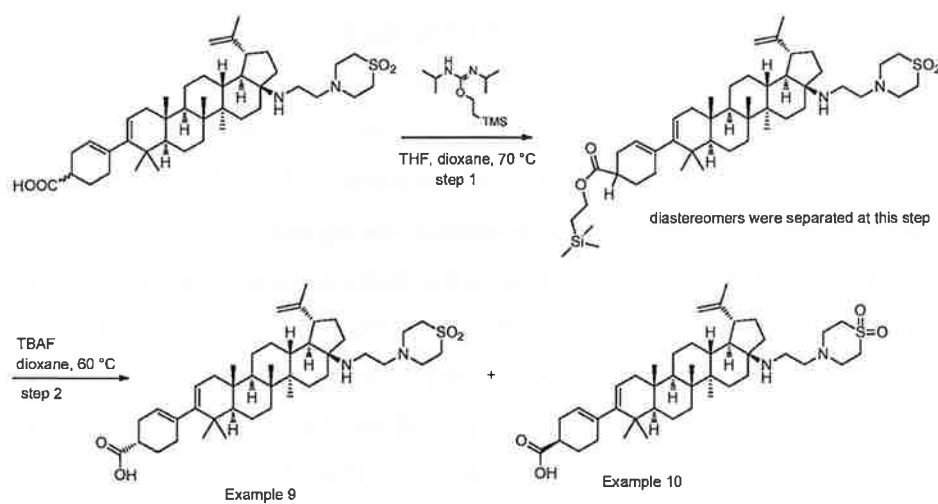
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.1 g, 0.177 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.125 g, 0.532 mmol), potassium iodide (0.088 g, 0.532 mmol) and phosphoric acid, potassium salt (0.188 g, 0.887 mmol). The mixture was diluted with acetonitrile (2 mL) and flushed with nitrogen, then the vial was
- 10 sealed and heated to 100 °C for 15.5h. The mixture was cooled to rt and was diluted with water (20 mL) then was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was adsorbed to silica gel, then was purified by flash chromatography using a 20-50% ethyl acetate in hexanes gradient and a 25g silica gel
- 15 column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give ethyl 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-
- 20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.059 g, 0.081 mmol, 45.9 % yield) as an off-white foam. LCMS: m/e 725.6 (M+H)⁺, 2.24 min (method 1).

- Step 3:** To a solution of ethyl 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-
- 25 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.059 g, 0.081 mmol) in 1,4-dioxane (2 mL) was added sodium hydroxide (1N) (0.407 mL, 0.407 mmol). The mixture was heated to 70 °C for 16h then was cooled to rt. The mixture was purified by prep HPLC (method 3, retention time: 5.7 minutes). The fractions containing the expected
- 30 product were combined and concentrated under reduced pressure to give the expected product. Minor impurities remained, so a second purification by prep HPLC followed (method 4, retention time: 12.7 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-

((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (0.012 g, 0.015 mmol, 18.5 % yield) as a white solid. LCMS: m/e 697.6 (M+H)⁺, 1.92 min (method 1). ¹H NMR (400MHz, acetic acid-d₄) δ = 5.37 (br. s., 1H), 5.23 (d, J =6.0 Hz, 1H), 3.41 (d, J =12.3 Hz, 1H), 3.35 - 3.02 (m, 11H), 2.63 - 2.54 (m, 1H), 1.22 (s, 3H), 1.06 (s, 3H), 0.89 (d, J =6.8 Hz, 3H), 0.81 (d, J =6.5 Hz, 3H), 2.40 - 0.76 (m, 39H).

Example 9 and Example 10

Preparation of (R)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA and (S)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



Step 1: Preparation and separation of the diastereomers of 2-(trimethylsilyl)ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-

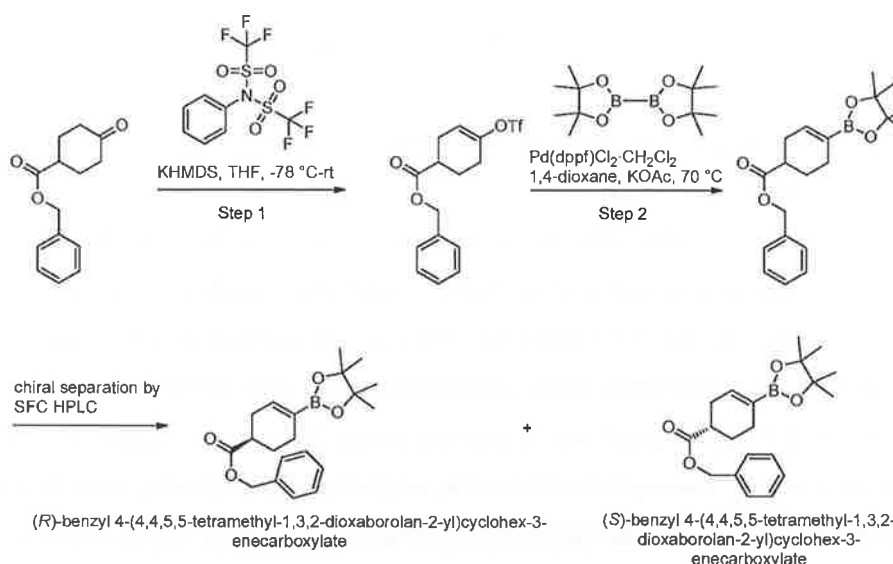
dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

- To a vial containing a suspension of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid (0.025 g, 0.036 mmol) in THF (1 mL) was added (Z)-2-(trimethylsilyl)ethyl N,N'-diisopropylcarbamimidate (0.017 g, 0.070 mmol). The vial was sealed and heated to 70 °C and upon heating the solids
- completely dissolved. After 4.5h of heating, the mixture was cooled to rt. LC/MS showed a mixture of starting material and product present. Since the seal on the vial started to fail, 1 mL of 1,4-dioxane was added and the mixture was again heated to 70 °C. After heating the mixture for 21h (total), the mixture was cooled to rt. LC/MS still showed starting material present, so an additional 30 mg of (Z)-2-(trimethylsilyl)ethyl N,N'-diisopropylcarbamimidate was added and the mixture was further heated to 70 °C. After 7h of heating, the mixture was cooled to rt. The mixture was purified by flash chromatography using a 0-50% ethyl acetate in hexanes gradient and a 12g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give 2-(trimethylsilyl)ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.02 g, 0.025 mmol, 69.9 % yield) as a white foam. The mixture of diastereomers was separated by SFC (Chiral SFC Method 1) and the fractions containing each isolate was concentrated under reduced pressure to give 4.7 mg of isomer 1 and 6.1 mg of isomer 2. **Isomer 1:** ¹H NMR (400MHz, chloroform-d) δ = 5.35 (br. s., 1H), 5.18 (d, J=4.5 Hz, 1H), 4.71 (br. s., 1H), 4.59 (br. s., 1H), 4.21 - 4.14 (m, 2H), 3.16 - 2.95 (m, 8H), 2.75 - 2.39 (m, 6H), 2.30 (br. s., 2H), 2.17 (br. s., 2H), 1.69 (s, 3H), 1.06 (s, 3H), 0.98 (br. s., 3H), 0.96 (br. s., 3H), 0.90 (s, 3H), 0.86 (s, 3H), 2.04 - 0.83 (m, 27H), 0.065 - 0.04 (m, 9H). **Isomer 2:** ¹H NMR (400MHz, chloroform-d) δ = 5.35 (br. s., 1H), 5.21 - 5.16 (m, 1H), 4.71 (br. s., 1H), 4.60 (br. s., 1H), 4.21 - 4.14 (m, 2H), 3.14 - 2.97 (m, 8H), 2.74 - 2.42 (m, 6H), 2.30 (br. s.,

2H), 2.25 - 2.08 (m, 2H), 1.69 (s, 3H), 1.06 (s, 3H), 0.96 (br. s., 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.86 (s, 3H), 2.03 - 0.83 (m, 27H), 0.065 - 0.04 (m, 9H).

- Step 2.** To a solution of each of the two isomers in the previous step in 1,4-Dioxane (0.25 mL) was added TBAF (75% in water) (50 mg, 0.143 mmol). The mixtures were warmed to 60 °C. After 4.5h the mixtures were cooled to rt then was diluted with methanol and dioxane and were purified by prep HPLC (method 5, retention time: isomer 1: 9.7 minutes, isomer 2: 9.6 minutes). The fractions containing each product were combined and concentrated under reduced pressure to give the the free carboxylic acid of isomer 1 (2.4 mg, 2.9 μmol, 49% yield) and isomer 2 (4.5 mg, 5.5 μmol, 93 % yield) as off-white solids.
- Example 9: (R)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA: LCMS: m/e 695.6 (M+H)⁺, 1.65 min (method 1). ¹H NMR (400MHz, Acetic) δ = 5.38 (br. s., 1H), 5.23 (d, J=4.5 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 3.50 - 3.43 (m, 1H), 3.35 - 3.02 (m, 11H), 2.96 - 2.88 (m, 1H), 2.64 - 2.54 (m, 1H), 1.73 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.96 (br. s., 3H), 0.95 (br. s., 3H), 2.42 - 0.90 (m, 28H).**
- Example 10: (S)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA: LCMS: m/e 695.6 (M+H)⁺, 1.63 min (method 1). ¹H NMR (400MHz, Acetic) δ = 5.38 (br. s., 1H), 5.23 (d, J=5.5 Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.48 (d, J=11.8 Hz, 1H), 3.36 - 3.04 (m, 11H), 2.95 - 2.83 (m, 1H), 2.66 - 2.55 (m, 1H), 1.73 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H), 0.99 (s, 6H), 0.95 (s, 3H), 2.41 - 0.92 (m, 28H).**

Preparation and purification of (R)- and (S)-benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate



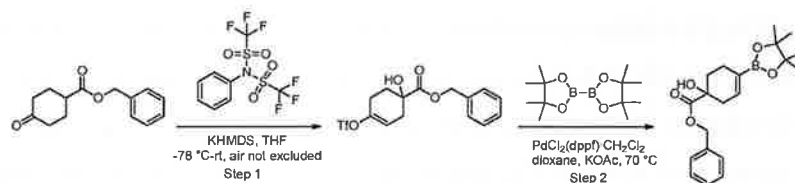
Step 1. Preparation of benzyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate

- 5 A rbf containing benzyl 4-oxocyclohexanecarboxylate (6.0 g, 25.8 mmol) (see *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5107-5110. for the preparation) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (10.15 g, 28.4 mmol) was evacuated and backfilled with nitrogen three times. The mixture was diluted with THF (100 mL) and was cooled to -78 °C. To the mixture was added KHMDS (0.5M in toluene) (64.6 mL, 32.3 mmol) slowly over 20 minutes. The mixture was stirred at -78 °C for 30
- 10 minutes then the ice bath was removed and it was stirred for 1.5h at rt. The mixture was diluted with water (150 mL) and was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude benzyl 4-
- 15 (((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate as a light-red oil. The crude product was used in the next step with no additional purification. ¹H NMR (500MHz, CHLOROFORM-d) δ = 7.42 - 7.29 (m, 5H), 5.79 - 5.76 (m, 1H), 5.18 - 5.13 (m, 2H), 2.70 - 2.61 (m, 1H), 2.52 - 2.34 (m, 4H), 2.20 - 2.13 (m, 1H), 1.99 - 1.90 (m, 1H).

- 20 **Step 2. Preparation of benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate**

To a flask containing the crude benzyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (9.40 g, 25.8 mmol) was added bis(pinacolato)diboron (6.88 g, 27.1 mmol), potassium acetate (6.33 g, 64.5 mmol), and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (0.637 g, 0.774 mmol). The mixture was evacuated and filled with nitrogen 3 times, then was diluted with 1,4-dioxane (100 mL) and was heated to 70 °C for 21.5h. The mixture was cooled to rt, diluted with water (100 mL), and extracted with ethyl acetate (3 x 100 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-30% ethyl acetate in hexanes gradient and a 300g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4.26g of the product as a clear, colorless oil. The sample was divided and one portion (1.0g) was purified a second time by flash chromatography using a 0-7% acetone in hexanes gradient. The fractions containing the product were combined and concentrated under reduced pressure to give 0.7g of benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as a clear, colorless oil. A second portion (2.9g), was purified by chiral SFC (chiral SFC method 2) to give the two separate enantiomers: **enantiomer 1**: (R)-benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate: 0.883g ; and **enantiomer 2**: (S)-benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate: 0.932g. ¹H NMR (500MHz, chloroform-d) δ = 7.42 - 7.32 (m, 5H), 6.59 - 6.55 (m, 1H), 5.15 (s, 2H), 2.65 - 2.58 (m, 1H), 2.42 - 2.37 (m, 2H), 2.34 - 2.26 (m, 1H), 2.20 - 2.03 (m, 2H), 1.71 - 1.59 (m, 1H), 1.28 (s, 12H).

Preparation of benzyl 1-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate



Step 1: Preparation of benzyl 1-hydroxy-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate

A rbf containing a solution of benzyl 4-oxocyclohexanecarboxylate (0.25 g, 1.076 mmol) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.481 g, 1.345 mmol) in THF (10 mL) was cooled to -78 °C. To the solution was added KHMDS (0.5M in toluene) (4.74 mL, 2.368 mmol) (Although the flask was fitted with a septum,
5 no special attention was made to exclude air from the reaction). The mixture was stirred at -78 °C for 1h then was warmed to rt and was stirred for 1.5h. TLC still showed a trace of starting material present, so an additional 0.1 g of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide was added and the mixture was further stirred at rt for 1h then the mixture was diluted with water (30 mL) and was extracted
10 with ethyl acetate (3 x 30 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 0-40% ethyl acetate in hexanes gradient and a 25g silica gel column. The fractions containing the major product were combined and concentrated under reduced pressure to give benzyl 1-hydroxy-4-
15 (((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (0.101 g, 0.266 mmol, 24.7% yield) as a clear film. ¹H NMR (500MHz, chloroform-d) δ = 7.43 - 7.32 (m, 5H), 5.70 (dt, J =5.0, 2.2 Hz, 1H), 5.24 (s, 2H), 3.17 (s, 1H), 2.82 - 2.75 (m, 1H), 2.72 - 2.63 (m, 1H), 2.40 - 2.28 (m, 2H), 2.13 (ddd, J =13.3, 10.9, 6.2 Hz, 1H), 1.96 (ddt, J =13.3, 6.0, 2.6 Hz, 1H).

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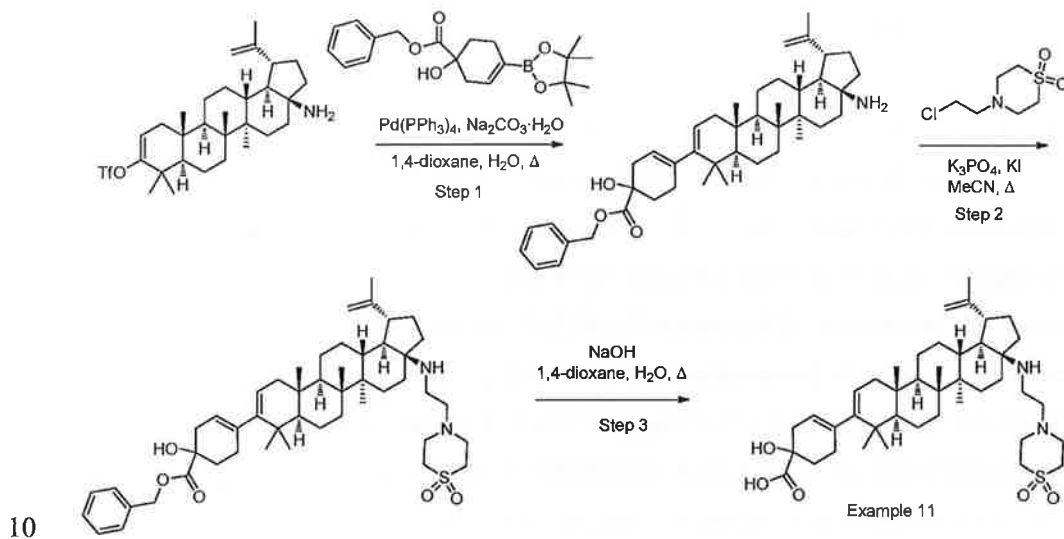
Step 2. Preparation of benzyl 1-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate

To a flask containing benzyl 1-hydroxy-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (0.1 g, 0.263 mmol) was added bis(pinacolato)diboron (0.070 g, 0.276
25 mmol), potassium acetate (0.065 g, 0.657 mmol), and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (6.49 mg, 7.89 μ mol). The mixture was diluted with 1,4-dioxane (2mL), flushed with nitrogen, and heated to 70 °C for 16h. The mixture was cooled to rt, diluted with water (20 mL), and was extracted
30 with ethyl acetate (3 x 20 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give crude benzyl 1-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-

enecarboxylate. 113 mg of crude product were carried to the next step with no additional purification. LCMS: m/e 359.3 ($M+H$)⁺, 1.79 min (method 1).

Example 11

- 5 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylic acid, TFA



Step 1: Preparation of benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylate

A flask containing benzyl 1-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.113 g, 0.221 mmol) and (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.082 g, 0.147 mmol) was diluted with 1,4-dioxane (1 mL) and water (0.25 mL). To the mixture was added sodium carbonate hydrate (0.075 g, 0.605 mmol) and the mixture was degassed with nitrogen for

five minutes. To the mixture was added palladium tetrakis (5.10 mg, 4.41 μ mol) then the flask was purged then refilled with nitrogen three times. The mixture was heated to 85 °C for 4h then was cooled to rt and was purified by flash chromatography using a 20-80% ethyl acetate in hexanes gradient and a 25g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylate (0.053g, 0.083 mmol, 56.3% yield) as an off-white foam. LCMS: m/e 640.6 (M+H)⁺, 1.91 min (method 1).

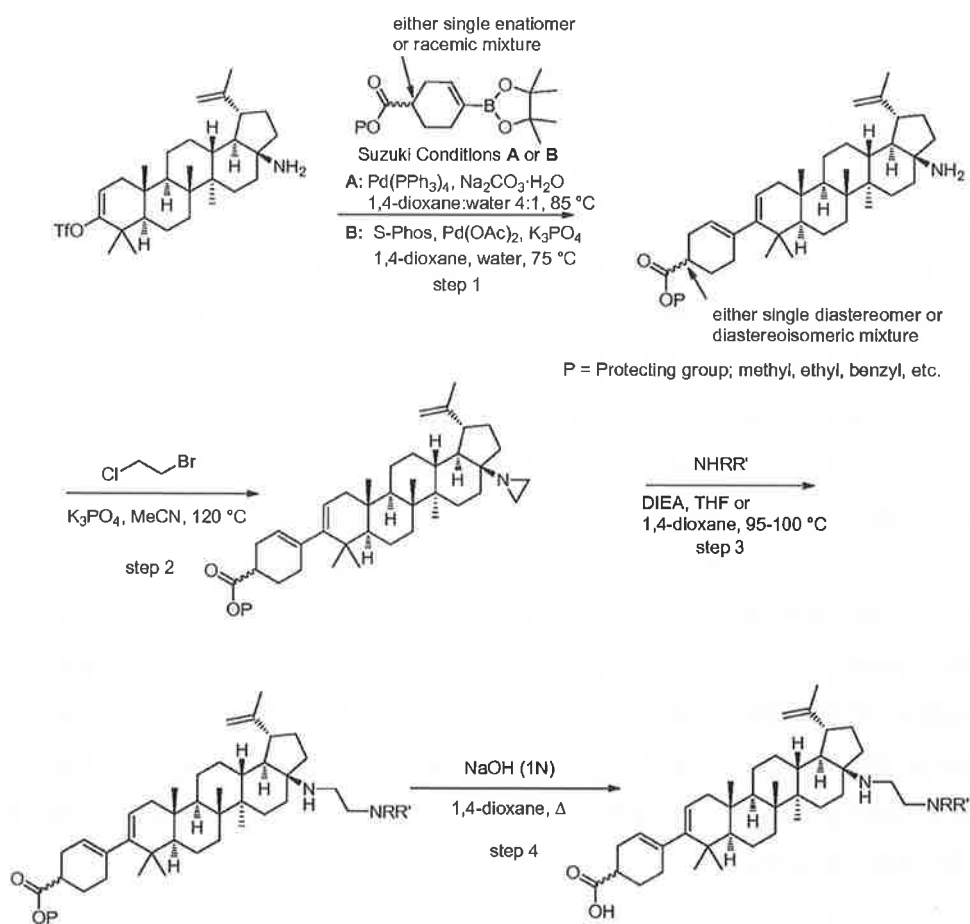
Step 2: Preparation of benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylate

To a sealable vial was added benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylate (0.053 g, 0.083 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide, HCl (0.078 g, 0.331 mmol), potassium iodide (0.041 g, 0.248 mmol) and phosphoric acid, potassium salt (0.088 g, 0.414 mmol). The mixture was diluted with acetonitrile (1.5 mL) and flushed with nitrogen, then was sealed and heated to 100 °C for 15.25 h. The mixture was cooled to rt and was filtered to remove the solids which were washed with dichloromethane. The filtrate was concentrated under reduced pressure and adsorbed to silica gel, then was purified by flash chromatography using a 20-80% ethyl acetate in hexanes gradient and a 12g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylate (0.029 g, 0.036 mmol, 43.7 % yield) as a clear, colorless film. LCMS: m/e 801.7 (M+H)⁺, 1.92 min (method 1).

Step 3: To a solution of benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

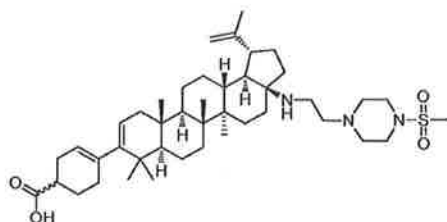
- 5 cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylate (28.8 mg, 0.036 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.2 mL, 0.200 mmol). The mixture was heated to 75 °C for 4.5h then was cooled to rt. The mixture was diluted with methanol and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-
- 10 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-hydroxycyclohex-3-enecarboxylic acid, TFA (16 mg, 0.018 mmol, 51.2 % yield) as a white solid. LCMS: m/e 711.6 (M+H)⁺, 1.54 min
- 15 (method 1) ¹H NMR (500MHz, acetic acid-d₄) δ = 5.33 (br. s., 1H), 5.32 - 5.28 (m, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.50 (dt, J=12.8, 3.3 Hz, 1H), 3.36 - 3.06 (m, 11H), 2.93 - 2.86 (m, 1H), 2.75 - 2.69 (m, 1H), 2.52 - 2.39 (m, 1H), 1.76 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 2.34 - 0.93 (m, 35H).

20 **General Procedure for C-3 cyclohexene, C-17 amine formation (Examples 12-16)**



Example 12

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



Step 1. Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

- 5 To a flask containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (1.22 g, 2.187 mmol) was added phosphoric acid, potassium salt (1.393 g, 6.56 mmol), ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.613 g, 2.187 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-phos) (0.067 g, 0.164 mmol), and palladium(II)acetate (0.025 g, 0.109 mmol). The mixture was diluted with 1,4-dioxane (10 mL) and water (1 mL), was flushed with nitrogen, then was sealed and heated to 75 °C. After 15h of heating, the mixture was cooled to rt and was concentrated under reduced pressure. The residue was diluted with water (40 mL) and was extracted with ethyl acetate (3 x 50 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 10-70% EtOAc in hexanes gradient and an 80g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (806 mg, 1.434 mmol, 65.6 % yield) as an off-white solid. LCMS: m/e 562.7 (M+H)⁺, 2.17 min (method 1).

Step 2. Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

- 30 To a sealable vial was added ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.1 g, 0.178 mmol), 1-bromo-2-

chloroethane (0.148 mL, 1.780 mmol) and phosphoric acid, potassium salt (0.189 g, 0.890 mmol). The mixture was diluted with acetonitrile (1.5 mL), was flushed with nitrogen, then was sealed and heated to 120 °C. After 17.5h of heating, the mixture was cooled to rt and some of the solids were removed by filtration. The filtrate was

5 concentrated under reduced pressure to give ethyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as the crude product which was used in the next step with no additional purification. LCMS: m/e

10 588.7 (M+H)⁺, 2.30 min (method 1).

Step 3. Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

15 To a flask containing the crude ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.094 g, 0.16 mmol), was added

20 1-Methanesulfonyl-piperazine (0.131 g, 0.800 mmol). The mixture was diluted with 1,4-dioxane (2 mL) and Hunig's base (0.168 mL, 0.960 mmol) was added. The mixture was attached to a reflux condensor and was heated to 100 °C for 24h then was cooled to rt, concentrated under reduced pressure, and adsorbed to silica gel. The mixture was purified by flash chromatography using a 12g silica gel column and a 20-80% ethyl

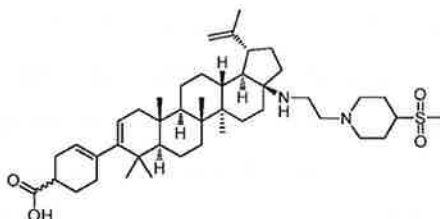
25 acetate in hexanes gradient. The fractions containing the product were combined and concentrated under reduced pressure to give ethyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as an off-white solid. LCMS: m/e

30 752.8 (M+H)⁺, 2.22 min (method 1).

Step 4. To a solution of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (75 mg, 0.100 mmol) in 1,4-dioxane (2 mL) was added sodium hydroxide (1N) (0.499 mL, 0.499 mmol). The mixture was heated to 75 °C for 3h then was cooled to rt, and was purified by prep HPLC (method 8, retention time: 9.2 minutes). The fractions containing the expected product were combined and were concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (51 mg, 0.061 mmol, 61% yield) as a white solid. LCMS: m/e 724.7 (M+H)⁺, 1.72 min (method 1). ¹H NMR (500MHz, acetic acid-d₄) δ = 5.38 (br. s., 1H), 5.25 - 5.21 (m, 1H), 4.83 (s, 1H), 4.72 (s, 1H), 3.69 - 3.49 (m, 8H), 3.36 (br. s., 4H), 2.92 (s, 3H), 2.87 - 2.78 (m, 1H), 2.64 - 2.56 (m, 1H), 1.73 (s, 3H), 1.17 (s, 3H), 1.08 (s, 3H), 2.39 - 0.84 (m, 37H)

Example 13

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



Steps 1 and 2 are the same described above in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA.

Step 3: Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a flask containing a suspension of the crude ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.055 g, 0.094 mmol) in 1,4-dioxane (2 mL) was added Hunig's base (0.098 mL, 0.561 mmol) followed by 4-(methylsulfonyl)piperidine (0.076 g, 0.468 mmol). The mixture was heated to 100 °C for 20.5h then was cooled to rt and was purified by flash chromatography using a 20-80% ethyl acetate in hexanes gradient and a 12g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.036g, 0.048 mmol, 51.2% yield) as an off-white solid. LCMS: m/e 751.7 (M+H)⁺, 2.29 min (method 1).

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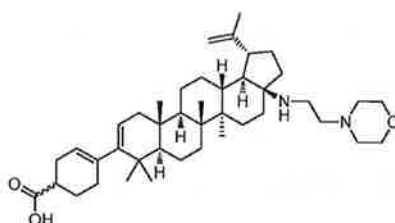
Step 4: To a solution of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.036 g, 0.048 mmol) in 1,4-dioxane (2 mL) was added sodium hydroxide (1N) (0.240 mL, 0.240 mmol) and the mixture was heated to 75 °C. After 24h of heating the mixture was cooled to rt and was stirred for an additional 24h, then was diluted with methanol and dioxane and was purified by prep HPLC (method 9, retention time: 10.96 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

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cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (0.026 g, 0.031 mmol, 65 % yield) as a white solid. LCMS: m/e 723.7 (M+H)⁺, 1.65 min (method 1).

Example 14

- 5 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



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Steps 1 and 2 are the same described above in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA.

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Step 3: Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

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To a flask containing a suspension of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.202 g, 0.344 mmol) in 1,4-dioxane (3 mL) was added Hunig's base (0.421 mL, 2.408 mmol) followed by morpholine (0.150 mL, 1.720 mmol). The mixture was heated to 100 °C for 15.5h then was cooled to rt. The mixture was directly purified by flash chromatography using a 0-40% ethyl acetate in hexanes gradient and a 25g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced

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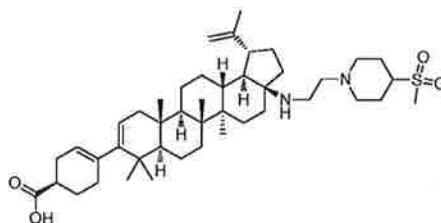
pressure to give ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.148 g, 0.219 mmol, 63.7 %
5 yield) as a white foam. LCMS: m/e 675.8 (M+H)⁺, 2.06 min (method 1).

Step 4: To a solution of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.02 g, 0.030 mmol) in 1,4-dioxane (1 mL) was added sodium hydroxide (1N) (0.148 mL, 0.148 mmol) and the mixture was heated to 75 °C. After heating the mixture for 17.5h, it was cooled to rt and was purified by prep HPLC (method 8, retention time: 8.6 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure
15 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (19 mg, 0.025 mmol, 83 % yield) as a white solid. LCMS: m/e 647.7 (M+H)⁺, 1.69 min (method 1). ¹H NMR
20 (500MHz, acetic acid-d₄) δ = 5.41 (br. s., 1H), 5.28 - 5.23 (m, 1H), 4.85 (s, 1H), 4.74 (s, 1H), 3.97 (br. s., 4H), 3.80 - 3.67 (m, 4H), 3.41 (br. s., 4H), 2.87 - 2.77 (m, 1H), 2.66 - 2.59 (m, 1H), 1.76 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.06 - 0.93 (m, 9H), 2.44 - 0.74 (m, 28H).

25 Example 15

Preparation of (R)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA

30



Step 1. Preparation of (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

- To a vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.65 g, 1.165 mmol) was added phosphoric acid, potassium salt (0.742 g, 3.50 mmol), (R)-benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.8 g, 2.338 mmol) (enantiomer 1 prepared above), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-phos) (0.072 g, 0.175 mmol) and palladium(II) acetate (0.026 g, 0.117 mmol). The mixture was diluted with 1,4-dioxane (10 mL) and water (1 mL), flushed with nitrogen, then the vial was sealed and heated to 75 °C. After 6h of heating, the mixture was cooled to rt, diluted with water (20 mL) and brine (20 mL), and was extracted with dichloromethane (5 x 40 mL). The organic layers were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 10-60% ethyl acetate in hexanes gradient and a 40g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.488 g, 0.782 mmol, 67.1 % yield) as an off-white solid. LCMS: m/e 624.65 (M+H)⁺, 2.18 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 7.40 - 7.30 (m, 5H), 5.35 (br. s., 1H), 5.18 (dd, J=6.2, 1.8 Hz, 1H), 5.14 (s, 2H), 4.73 (d, J=2.0 Hz, 1H), 4.60 (s, 1H), 2.65 - 2.50 (m, 2H), 2.38 -

2.30 (m, 2H), 2.25 - 1.94 (m, 5H), 1.70 (s, 3H), 1.07 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.86 (s, 3H), 1.80 - 0.83 (m, 23H).

Step 2. Preparation of (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a scalable vial was added (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.075 g, 0.120 mmol), 1-bromo-2-chloroethane (0.100 mL, 1.202 mmol), and phosphoric acid, potassium salt (0.128 g, 0.601 mmol). The mixture was diluted with acetonitrile (1.5 mL), flushed with nitrogen, then the vial was sealed and heated to 120 °C. After 24h of heating, the mixture was cooled to rt and was filtered to remove solids. The solids were washed with dichloromethane and the filtrate was concentrated under reduced pressure to give (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as an off-white solid that was used in the next step with no additional purification. LCMS: m/e 650.7 (M+H)⁺, 2.22 min (method 1).

Step 3. Preparation of (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate, TFA

To a Flask containing a suspension of (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (78 mg, 0.12 mmol) in 1,4-dioxane (2 mL) was added Hunig's base (0.126 mL, 0.720 mmol) and 4-(methylsulfonyl)piperidine (98 mg, 0.600 mmol). The flask was heated to 100 °C with a reflux condensor attached for 23h, then was cooled to rt, diluted with water (10 mL) and

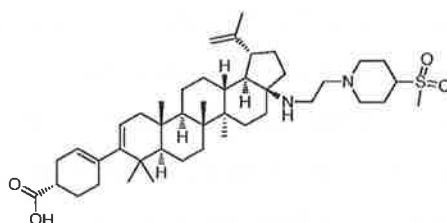
extracted with dichloromethane (3 x 10 mL). The organic layers were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method 10). The fractions containing the expected product were combined and were concentrated under a stream of nitrogen to give (R)-benzyl 4-

- 5 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate, TFA (44.5 mg, 0.048 mmol, 40.0 % yield) as a white foam. LCMS: m/e 813.75 (M+H)⁺, 2.09 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 7.39 - 7.30 (m, 5H), 5.35 (br. s., 1H), 5.17 (d, J=4.6 Hz, 1H), 5.14 (s, 2H), 4.78 (s, 1H), 4.70 (s, 1H), 3.45 - 3.21 (m, 5H), 3.19 - 3.09 (m, 1H), 3.07 - 2.98 (m, 1H), 2.90 (s, 3H), 2.81 - 2.54 (m, 4H), 1.69 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H), 2.40 - 0.82 (m, 32H).

- 15 **Step 4.** To a solution of (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.04 g, 0.049 mmol) in 1,4-dioxane (2 mL) was added sodium hydroxide (1N) (0.246 mL, 0.246 mmol). The mixture was heated to 60 °C for 5h, then was cooled to rt. The mixture was diluted with methanol and dioxane and was purified by prep HPLC (method 11, retention time: 8.89 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give (R)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (27 mg, 0.032 mmol, 65 % yield) as a white solid. LCMS: m/e 723.8 (M+H)⁺, 2.02 min (method 1). ¹H NMR (500MHz, acetic acid-d₄) δ = 5.41 (br. s., 1H), 5.26 (d, J=4.6 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.87 - 3.68 (m, 6H), 3.47 - 3.39 (m, 1H), 3.23 (q, J=9.8 Hz, 2H), 3.02 (s, 3H), 2.86 - 2.78 (m, 1H), 2.67 - 2.59 (m, 1H), 1.76 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 2.49 - 0.87 (m, 32H). The structure of this compound was confirmed by X-Ray crystallography.

Example 16

Preparation of (S)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



Step 1. Preparation of (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate.

To a vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.05 g, 0.090 mmol) was added phosphoric acid, potassium salt (0.057 g, 0.269 mmol), (S)-benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.062 g, 0.181 mmol) (enantiomer 2 prepared above), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-phos) (5.52 mg, 0.013 mmol), and palladium(II) acetate (2.013 mg, 8.96 μ mol). The mixture was diluted with 1,4-dioxane (1 mL) and water (0.1 mL), was flushed with nitrogen, then was sealed and heated to 75 °C. After 6h of heating, the mixture was cooled to rt, was diluted with dichloromethane, and was dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography using a 10-60% ethyl acetate in hexanes gradient and a 12g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.042 g, 0.067 mmol, 75 % yield) as an off-white solid. ¹H NMR (500MHz, chloroform-d) δ = 7.42 - 7.31 (m, 5H), 5.37 (br. s., 1H), 5.21 - 5.17 (m, 1H), 5.16 (s, 2H), 4.75 (d, J =1.9 Hz, 1H), 4.62 (s, 1H), 2.65 - 2.52 (m, 2H), 2.39 - 2.32 (m, 2H), 2.22 - 2.15 (m, 2H), 2.10 - 1.96 (m, 3H), 1.71 (s, 3H),
5 1.09 (s, 3H), 0.98 (s, 6H), 0.91 (s, 3H), 0.88 (s, 3H), 1.82 - 0.83 (m, 23H).

Step 2. Preparation of (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a sealable vial was added (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.042 g, 0.067 mmol), 1-bromo-2-chloroethane (0.056 ml, 0.673 mmol) and phosphoric acid, potassium salt (0.071 g, 0.337 mmol). The mixture was diluted with acetonitrile (1 mL), was flushed with nitrogen, then was sealed and heated to 120 °C. After 23 h of heating, the mixture was cooled to rt and the reaction mixture was filtered to remove solids. The solids were washed with dichloromethane and the filtrate was concentrated under reduced pressure to give (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as an off-white solid. The crude product was used in the next step with no additional purification.
LCMS: m/e 650.8 (M+H)⁺, 2.26 min (method 1).

25

Step 3. Preparation of (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

To a flask containing a suspension of (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.044 g, 0.067

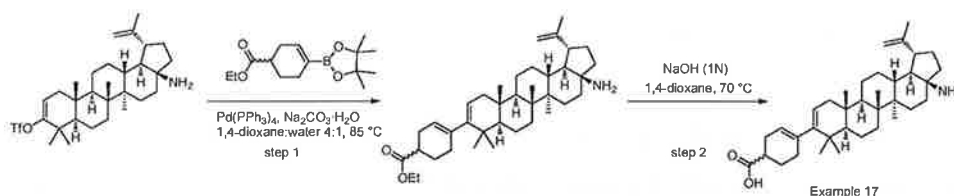
mmol) in 1,4-dioxane (2 mL) was added Hunig's base (0.070 mL, 0.402 mmol) followed by 4-(methylsulfonyl)piperidine, HCl (0.067 g, 0.335 mmol). The flask attached to a reflux condensor and was heated to 95 °C for 15h, then was cooled to rt. The crude mixture was adsorbed to silica gel and was purified by flash chromatography using a 10-
5 75% ethyl acetate in hexanes gradient and a 12g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
10 cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.033 g, 0.041 mmol, 60.6 % yield) as a clear, colorless film. LCMS: m/e 813.8 (M+H)⁺, 2.17 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 7.40 - 7.29 (m, 5H), 5.37 - 5.33 (m, 1H), 5.16 (dd, J=6.1, 1.7 Hz, 1H), 5.14 (s, 2H), 4.71 (d, J=1.7 Hz, 1H), 4.59 (s, 1H), 3.17 - 3.06 (m, 2H), 2.83 (s, 3H), 2.86 - 2.78 (m, 1H), 2.65 - 2.53 (m, 4H), 2.49 - 2.42 (m, 2H), 2.38 - 2.30 (m,
15 2H), 2.19 - 2.12 (m, 4H), 1.69 (s, 3H), 1.08 (s, 3H), 0.96 (s, 6H), 0.89 (s, 3H), 0.85 (s, 3H), 2.12 - 0.82 (m, 29H).

Step 4. To a solution of (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
20 cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.033 g, 0.041 mmol) in 1,4-dioxane (2 mL) was added sodium hydroxide (1N) (0.203 mL, 0.203 mmol). The mixture was heated to 60 °C for 4h then was cooled to rt. The mixture was diluted with methanol, was filtered through a plug of glass wool and was purified by prep HPLC (method 8,
25 retention time: 8.44 minutes). The fractions containing the expected product were combined and concentrated under reduced pressure to give (S)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
30 cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (21.0 mg, 0.025 mmol, 61 % yield) as a white solid. LCMS: m/e 723.6 (M+H)⁺, 1.57 min (method 1). ¹H NMR (500MHz, acetic acid-d₄) δ = 5.41 (br. s., 1H), 5.25 (d, J=4.7 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.83 - 3.67 (m, 6H), 3.44 - 3.37 (m, 1H), 3.22 - 3.12 (m, 2H), 3.02 (s, 3H), 2.87 -

2.78 (m, 1H), 2.66 - 2.59 (m, 1H), 2.44 - 2.32 (m, 3H), 1.76 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 2.28 - 0.90 (m, 29H).

Example 17

- 5 **Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, HCl**



10

- Step 1: Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate**

- 15 To a sealable vial containing (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.25 g, 0.448 mmol) was added
20 ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.138 g, 0.493 mmol), sodium carbonate hydrate (0.167 g, 1.345 mmol), and palladium tetrakis (0.016 g, 0.013 mmol). The mixture was diluted with 1,4-dioxane (4 mL) and water (1 mL) then was flushed with nitrogen and was sealed and heated to 85 °C in an oil bath. After 5h of heating, the mixture was cooled to rt, diluted with water (20 mL), and
25 extracted with ethyl acetate (3 x 20 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using a 6-50% ethyl acetate in hexanes gradient and 40g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give ethyl 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.119 g, 0.212 mmol, 47.3 % yield) as an off-white solid. LCMS: m/e 562.6 (M+H)⁺, 2.13 min (method 1). ¹H NMR (500MHz, chloroform-d) δ = 5.35 (br. s., 1H), 5.19 (d, J=6.1 Hz, 1H), 4.73 (d, J=1.9 Hz, 1H), 4.60 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 2.58 - 2.47 (m, 2H), 2.33 - 2.27 (m, 2H), 2.23 - 1.94 (m, 6H), 1.70 (s, 3H), 1.27 (t, 3H), 1.07 (s, 3H), 1.79 - 0.82 (m, 34H).

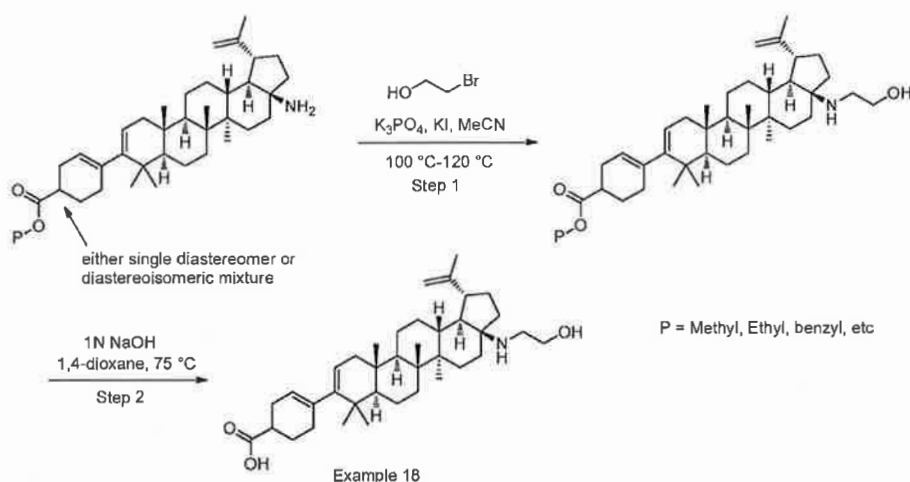
Step 2: To a suspension of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.02 g, 0.036 mmol) in 1,4-dioxane (1 mL) was added sodium hydroxide (1N) (0.2 mL, 0.200 mmol) and the mixture was heated to 70 °C. After heating the mixture for 15.5h, it was cooled to rt. The mixture was diluted with methanol and solids were apparent. 2 mL of 1N HCl were added and the solids that formed were collected by filtration and washed with water. The expected product, 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, HCl (0.02 g, 0.033 mmol, 94 % yield), was isolated as an off-white solid. LCMS: m/e 534.6 (M+H)⁺, 1.74 min (method 1). ¹H NMR (500MHz, Acetic acid-d₄) δ = 5.41 (br. s., 1H), 5.27 - 5.24 (m, 1H), 4.88 (s, 1H), 4.74 (s, 1H), 2.88 - 2.79 (m, 1H), 2.67 - 2.59 (m, 1H), 1.77 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H), 2.43 - 0.92 (m, 37H).

25

Example 18

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA

30



Step 1: Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

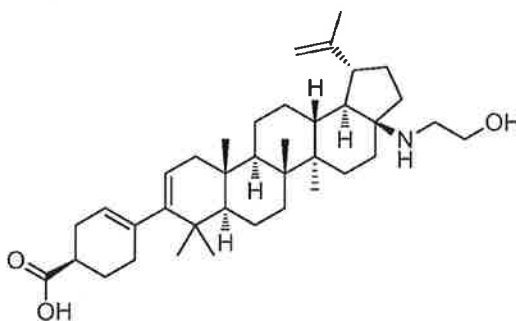
- To a sealable vial was added ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.156 g, 0.278 mmol), ethylene bromohydrin (0.059 mL, 0.833 mmol), potassium iodide (0.138 g, 0.833 mmol), and phosphoric acid, potassium salt (0.295 g, 1.388 mmol). The mixture was diluted with acetonitrile (2 mL), was flushed with nitrogen, then was sealed and heated to 100 °C. After 15h of heating, the mixture was cooled to rt. LC/MS still showed starting material present, so an additional 0.059 mL of ethylene bromohydrin was added, the mixture was diluted with 1 mL of acetonitrile, and it was sealed and heated to 120 °C. After heating the mixture for an additional 20h, it was cooled to rt, and diluted with 10 mL of water. The solids that formed were collected by filtration and were washed with water to give ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.145 g, 0.239 mmol, 86 % yield) as an off-white solid. LCMS: m/e 606.7 (M+H)⁺, 2.18 min (method 1).

- Step 2.** To a solution of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate (0.013 g, 0.022 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.2 mL, 0.200 mmol). The mixture was heated to 75 °C for 15h then was cooled to rt. The mixture was purified by prep HPLC (method 6, retention time: 14.0 minutes) and the fractions containing the product were combined and concentrated under reduced pressure. The product was purified a second time by prep HPLC (method 7, retention time: 16.9 minutes) to attain a higher level of purity.
- The fractions containing each product were concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA (4.6 mg, 6.6 μmol, 30 % yield). LCMS: m/e 578.6 (M+H)⁺, 1.71 min (method 1). ¹H NMR (500MHz, acetic acid-d₄) δ = 5.38 (br. s., 1H), 5.25 - 5.21 (m, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.05 - 3.93 (m, 2H), 3.42 - 3.36 (m, 1H), 3.32 - 3.24 (m, 1H), 2.85 (td, J=10.9, 5.3 Hz, 1H), 2.64 - 2.56 (m, 1H), 1.74 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.03 - 0.90 (m, 9H), 2.40 - 0.89 (m, 29H).
- The pure diastereomers were prepared by this method only using (R)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as starting material in step 1 for Example 19 and (S)-benzyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as starting material in step 1 for Example 20. Alternatively, they can be separated from the mixture described above.

Example 19

- Preparation of (R)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-**

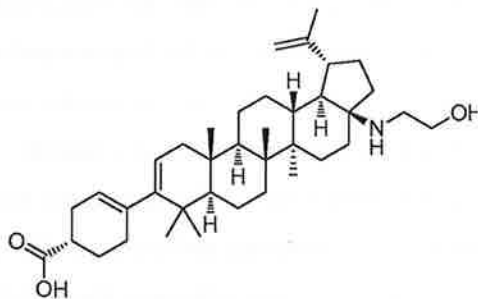
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



LCMS: m/e 578.7 (M+H)⁺, 1.75 min (method 1). ¹H NMR (500MHz, acetic acid-d₄) δ =
 5.38 (br. s., 1H), 5.22 (dd, J =6.1, 1.6 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.06 - 3.94 (m,
 2H), 3.42 - 3.37 (m, 1H), 3.32 - 3.25 (m, 1H), 2.86 (td, J =11.0, 5.5 Hz, 1H), 2.63 - 2.56
 (m, 1H), 1.74 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H),
 2.41 - 0.85 (m, 29H).

10 Example 20

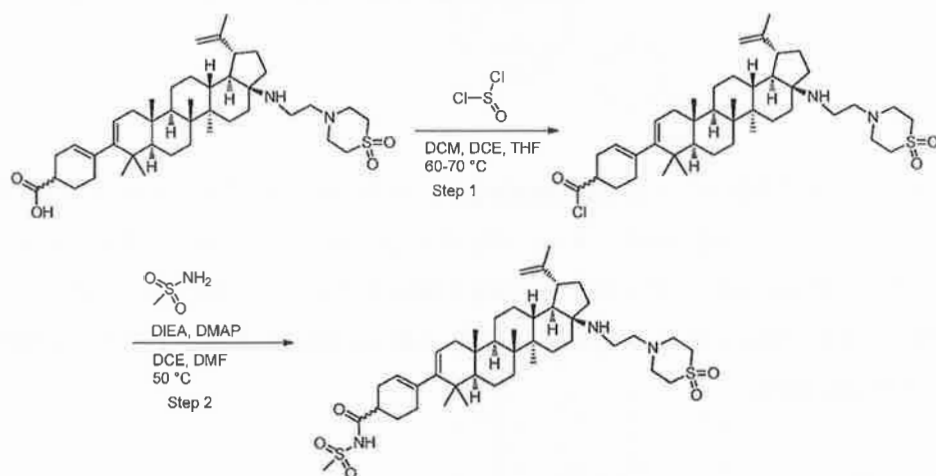
Preparation of (S)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid, TFA



LCMS: m/e 578.6 (M+H)⁺, 1.67 min (method 1). ¹H NMR (500MHz, Acetic acid-d₄) δ =
 5.38 (br. s., 1H), 5.23 (d, J =4.9 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.05 - 3.91 (m, 2H),
 3.39 - 3.33 (m, 1H), 3.30 - 3.24 (m, 1H), 2.92 - 2.83 (m, 1H), 2.64 - 2.56 (m, 1H), 1.74 (s,
 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 2.41 - 0.83 (m,
 29H).

Example 21

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-N-(methylsulfonyl)cyclohex-3-enecarboxamide, TFA



**Step 1. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 10 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarbonyl chloride.**

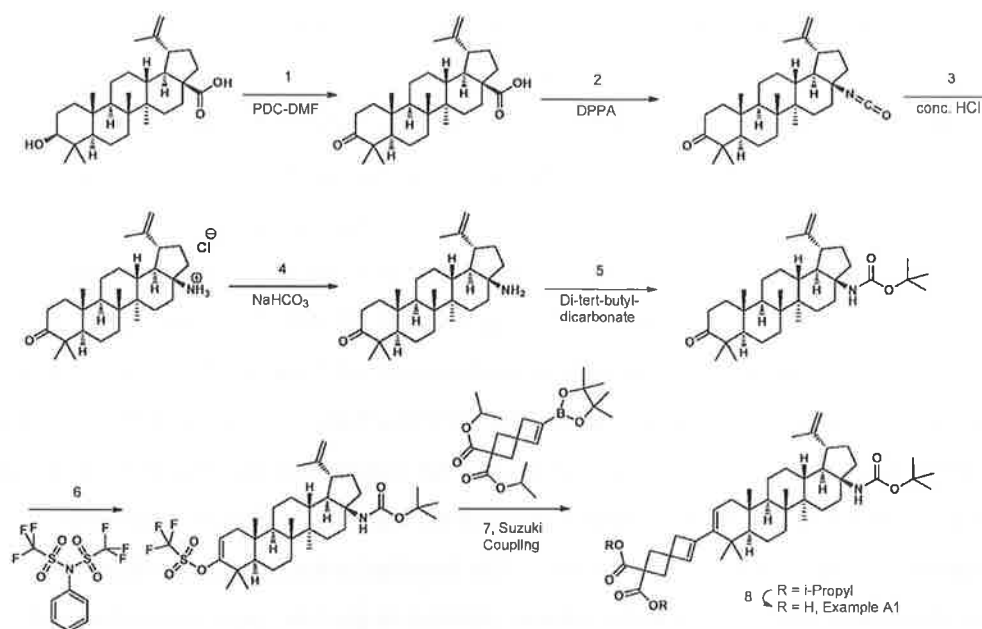
To a suspension of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 15 cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid (0.1 g, 0.144 mmol) in dichloromethane (4 mL) was added thionyl chloride (0.105 mL, 1.439 mmol). The mixture was attached to a reflux condensor and was heated to reflux. The solids did not completely dissolve, so DCE (3 mL) was added and the mixture was warmed to 60 °C with a reflux condensor attached. Solids still remained, so THF (2 mL) was added and
 20 the mixture was further heated to 70 °C. The solids never completely dissolved, but the reaction was allowed to reflux regardless. After 4h of heating, the mixture was cooled to rt. LC/MS showed the methyl ester since methanol was added to analytical sample to help solubilize the product for analysis. The mixture was concentrated under reduced pressure, then was diluted with dichloromethane and concentrated two additional times.

The crude product was used in the next step with no additional purification. LCMS: m/e 709.7 (M+MeOH)⁺, 2.08 min (method 1).

- Step 2.** To a suspension of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarbonyl chloride (103 mg, 0.144 mmol) in 1,2-dichloroethane (3 mL) was added Hunig'sBase (0.252 mL, 1.440 mmol). To the solution was added a solution of methanesulfonamide (68.5 mg, 0.720 mmol) (dried by azeotroping with toluene prior to use) in 1,2-dichloroethane (1.5 mL) and DMF (2 mL). DMAP (3.52 mg, 0.029 mmol) was added and the mixture was warmed to 50 °C for 40h. The mixture was diluted with ethanol and dioxane and was purified by prep HPLC (method 5, retention time: 9.2 minutes). The fractions containing the product were combined and concentrated under reduced pressure to give the expected product still contaminated with a small amount of the parent carboxylic acid. The product was repurified by prep HPLC (method 16, retention time: 10.6 minutes). The fractions containing the product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-N-(methylsulfonyl)cyclohex-3-enecarboxamide, TFA (10.4 mg, 0.011 mmol, 7.74 % yield) as a white solid. LCMS: m/e 772.5 (M+H)⁺, 1.70 min (method 1). ¹H NMR (400MHz, acetic acid-d₄) δ = 5.39 (br. s., 1H), 5.24 (d, J=5.8 Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.52 - 3.44 (m, 1H), 3.30 (s, 3H), 3.34 - 3.03 (m, 12H), 2.86 (d, J=4.8 Hz, 1H), 2.61 - 2.48 (m, 1H), 1.73 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 1.05 - 0.92 (m, 9H), 2.39 - 0.88 (m, 27H).

Example A1

- Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid**



Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid.

To a chilled solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (2.35 g, 5.15 mmol) in DMF (45 mL) at ~4 °C under nitrogen was added pyridinium dichromate (PDC 3.87 g, 10.29 mmol) in a single portion. The suspension was rapidly stirred, forming an orange solution, but rapidly changed into dark brownish with all the PDC dissolved into the reaction mixture. The reaction was kept in an ice bath, and was allowed to warm to RT slowly over 8 hours. Stirring continued for 48 hrs at RT thereafter. The PDC reaction mixture acquired a dull dark brownish appearance but no PPT was observed. The crude DMF reaction solution was poured into vigorously stirred ethyl acetate (400 mL) causing a PPT of a light brownish solid. The suspension was filtered through a short bed (~1" thick) of silica gel type-H in a large diameter filter funnel. The clear filtrate was washed with 0.1 N HCl (200 mL), then with water (3 x 200 mL). All the volatile solvents were removed, giving 2.1 gm (88%) as a white solid. MS: m/e 477.21 (M+Na)⁺, 6.2 min (method 9). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.76 (d, J=2.3 Hz, 1H), 4.63 (s, 1H), 3.06 - 2.98 (m, 1H), 2.55 - 2.37 (m, 2H), 2.28 (s,

2H), 1.99 (d, $J=6.5$ Hz, 2H), 1.95 - 1.87 (m, 1H), 1.71 (s, 3H), 1.64 (t, $J=11.4$ Hz, 2H), 1.59 - 1.20 (m, 16H), 1.08 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H).

Step 2: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one.

To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (2.1 g, 4.62 mmol) in dioxane (20 mL) was added diphenylphosphoryl azide (DPPA 1.294 mL, 6.00 mmol) and N,N-diisopropylethylamine (2.092 mL, 12.01 mmol) forming a clear solution. The mixture was stirred at RT for 40 minutes before it was immersed into an oil bath at 102 °C under a nitrogen atmosphere for 16 hrs. The crude mixture was evaporated to dryness, re-dissolved into 100 mL DCM, washed 3 times with water. The product was purified by silica gel chromatography eluted with mixture of 20% ethyl acetate in hexanes to give 1.91 gm (92% yield) of the title product. MS: m/e 452.35 ($M+H$)⁺, 5.58 min (method 10). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.76 (d, $J=2.0$ Hz, 1H), 4.66 - 4.64 (m, 1H), 2.60 - 2.47 (m, 2H), 2.43 (dd, $J=7.5$, 4.5 Hz, 1H), 2.11 (br. s., 1H), 1.96 - 1.77 (m, 5H), 1.76 - 1.70 (m, 1H), 1.69 (d, $J=0.5$ Hz, 3H), 1.64 - 1.42 (m, 10H), 1.42 - 1.29 (m, 4H), 1.23 - 1.15 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.96 (s, 6H).

Step 3: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-aminium chloride.

To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (2.1 g, 4.65 mmol) in dioxane (30 mL) at RT was added 7 mL conc. HCl over a period of 5 minutes. The clear solution was stirred for 10 minutes, forming a slightly turbid mixture. Stirring continued for a total of 6 hours and the reaction mixture turned into a 2-layer mixture. All the volatile solvents were removed under high vacuum. The dried, crude material was dissolved into DCM (15 mL), poured over a short bed (~1" thick) of silica gel type-H, washed with 500 mL, 20% ethyl acetate in hexanes, followed by a 2:1 mixture of DCM:Ethyl acetate (0.5 L). Upon concentration, a pale gum was

obtained. The material was dried under high vacuum to give 1.55 gm (72 % yield). MS: m/e 426.40 M⁺, 4.11 min (method 11). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.24 (br. s., 3H), 4.83 (br. s., 1H), 4.66 (br. s., 1H), 2.62 - 2.17 (m, 4H), 2.16 - 1.78 (m, 5H), 1.77 - 1.31 (m, 17H), 1.30 - 1.16 (m, 5H), 1.09 (s, 3H), 1.03 (s, 3H), 0.99 (br. s., 3H),
5 0.93 (s, 3H).

Step 4: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one.

- 10 To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-aminium chloride (462 mg, 1.000 mmol) in DCM (6 mL) was added saturated solution of sodium bicarbonate 10 mL. The 2-phase mixture was vigorously stirred, DCM layer separated, it was washed with another portion of 6 mL of saturated sodium bicarbonate solution. The
15 mixture was extracted with 10 mL DCM three times. The combine DCM fractions was finally washed with 5 mL DI water. Upon evaporation and drying, a thick semi-solid was isolated. This crude material was used in the next step without further purification.

Step 5: Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate.

- 20 To the free base, (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (394 mg, 0.926 mmol) in 2 mL of THF was added di-tert-butyl dicarbonate (400 mg, 2 mmol),
25 the resulting solution was stirred at RT for 48 hours. The reaction was worked up by adding 8 mL of a mixture made up of 4 mL 0.5 M HCl and 4 mL of a half saturated ammonium chloride solution. The organic residues were extracted into ethyl acetate (25 mL X 3), the combined organic extract was washed once with DI water (25 mL).
Evaporation of solvents gave 455 mg (93%) of the desired product suitable for the next
30 preparation without further purification. MS: m/e 548.45 (M+Na)⁺, 5.87 min (method 12). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.76 - 4.70 (m, 1H), 4.65 - 4.59 (m, 1H), 4.39 - 4.27 (m, 1H), 2.68 - 2.30 (m, 5H), 2.06 - 1.84 (m, 2H), 1.69 (s, 5H), 1.54 (s, 9H), 1.45 (s, 16H), 1.08 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H).

Step 6: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate.

The title compound was prepared as described above in method 2 for the preparation of intermediate 1, step 6 in 72.3% yield.

Step 7: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate.

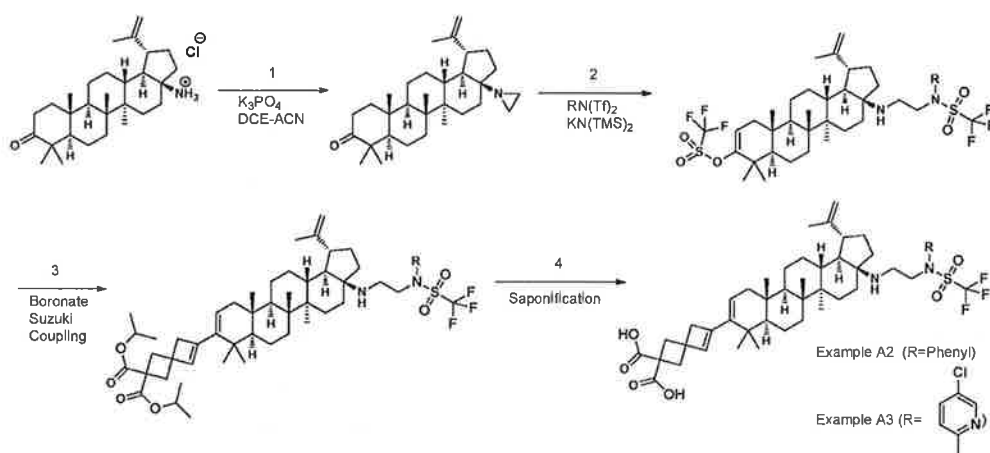
To a mixture of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (517 mg, 0.786 mmol), diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (364 mg, 0.928 mmol), sodium carbonate hydrate (292 mg, 2.358 mmol) and, tetrakis(triphenylphosphine)palladium (27.2 mg, 0.024 mmol) under nitrogen was added dioxane (4 mL) and water (1 mL) forming a very pale yellow suspension. The mixture was chilled to -78 °C, evacuation/purging (N₂) cycles were repeated three times. The reaction mixture was immersed into an oil bath at 85 °C and continued there for 2 hours. The reaction was quenched with 8 mL 1:1 mixture of 0.5N HCl and a half-saturated ammonium chloride solution. The organic residues were extracted into ethyl acetate (3 x 25 mL). The desired product was isolated by preparative HPLC using method 14 to afford the title compound (101 mg, 17%). MS: m/e 774.6 (M+H)⁺, 7.9 min (method 14). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.87 (br. s, 1H), 5.52 (dd, J=6.4, 1.9 Hz, 1H), 5.08 (dt, J=10.5, 6.2 Hz, 2H), 4.72 (s, 1H), 4.62 (d, J=1.5 Hz, 1H), 4.45 - 4.22 (m, 1H), 2.70 (s, 3H), 2.59 (d, J=2.3 Hz, 2H), 2.50 - 2.31 (m, 2H), 2.14 - 2.06 (m, 1H), 2.05 - 1.91 (m, 1H), 1.69 (s, 3H), 1.67 - 1.52 (m, 7H), 1.45 (s, 9H), 1.47 - 1.42 (m, 2H), 1.25 (m, 12H), 1.15 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.82 (s, 3H).

Step 8: To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-

((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (15 mg, 0.019 mmol) in dioxane (2 mL) and MeOH (1 mL) was added 1N NaOH (1 mL, 1 mmol). The mixture
 5 was stirred at 50 °C for 4 h. The solvent was removed in vacuo. The crude product was dissolved in dioxane (1 mL) and MeOH (1 mL). H₂O was added dropwise, the solid formed was collected by filtration to give desired product in 88% yield. MS: m/e 688.6 (M-H)⁻, 2.72 min (method 5). ¹H NMR (400MHz, METHANOL-d₄) δ 5.88 (s, 1H), 5.57 - 5.52 (m, 1H), 4.74 (d, J=1.8 Hz, 1H), 4.61 (s, 1H), 2.69 (s, 2H), 2.68 - 2.48 (m, 4H),
 10 2.33 - 2.25 (m, 1H), 2.14 (dd, J=17.9, 6.7 Hz, 1H), 1.99 - 1.83 (m, 2H), 1.77-0.81 (m, 19H), 1.70 (s, 3H), 1.45 (s, 9H), 1.16 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.86 (s, 3H).

Example A2 and Example A3

15 **Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(1,1,1-trifluoro-N-phenylmethylsulfonamido)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid and 6-**
 20 **((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(N-(5-chloropyridin-2-yl)-1,1,1-trifluoromethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid**



Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one.

A mixture of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-aminium chloride (1.09 g, 2.359 mmol) and potassium triphosphate (2.7 g, 12.72 mmol) in 1,2-dichloroethane (12 mL) and acetonitrile (24 mL) was placed in a thick-walled resealable vessel. The reaction vessel with its contents were flushed with nitrogen, sealed, and warmed to 130 °C for 36 hours. The crude reaction mixture was cooled to RT, filtered through a short bed (~1" thick) of silica gel type-H, washed with ethyl acetate (150 mL). The filtrate was concentrated into a free flowing solid (1.1 g, quantitative) which was taken to the next step without further purification. MS: m/e 452.35 (M+H)⁺, 3.12 min (method 21). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.77 (d, J=2.5 Hz, 1H), 4.62 (dd, J=2.5, 1.5 Hz, 1H), 2.74 - 2.56 (m, 2H), 2.55 - 2.36 (m, 3H), 2.10 - 2.00 (m, 1H), 1.96 - 1.86 (m, 1H), 1.85 - 1.75 (m, 1H), 1.74 - 1.67 (m, 2H), 1.68 (s, 3H), 1.55 - 1.24 (m, 16H), 1.16 - 1.10 (m, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.96 (d, J=2.8 Hz, 2H), 0.94 (s, 3H).

Step 2: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(N-(5-chloropyridin-2-yl)-1,1,1-trifluoromethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate.

(1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (353 mg, 0.781 mmol) was mixed with N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (338 mg, 0.860 mmol) in THF (2 mL) under nitrogen. The solution was stirred at -78 °C under nitrogen. A 0.5 M stock solution of potassium bis(trimethylsilyl)amide (1.875 mL, 0.938 mmol) was added, and the mixture was stirred at -78 °C for an hour. The desired product was purified by silica gel chromatography eluted with mixture of ethyl acetate and hexanes (230 mg, 35%). MS: m/e 844.3/846.3 (M+H)⁺, 6.47 min (method 15). ¹H NMR (400MHz, CHLOROFORM-d) δ (key fingerprint signals) 8.45 (d, J=2.0 Hz, 1H), 7.76 (dd, J=8.7, 2.6 Hz, 1H), 7.48 (d, J=8.5 Hz, 1H), 5.57 (d, J=6.5 Hz, 1H), 4.80 - 4.57 (m, 3H), 3.71 - 3.65 (m, 1H), 2.80 - 2.73 (m, 1H), 2.73 - 2.49 (m, 2H), 2.45 - 2.29 (m, 1H), 2.26 - 2.12 (m, 2H), 2.08 - 1.94 (m, 2H), 1.93 - 1.80 (m, 2H), 1.80 - 1.72 (m, 3H), 1.71 - 1.65 (m, 6H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -74.84 (s), -74.85 (s).

15

Step 3: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(N-(5-chloropyridin-2-yl)-1,1,1-trifluoromethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate.

20

(1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(N-(5-chloropyridin-2-yl)-1,1,1-trifluoromethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (226 mg, 0.268 mmol) was coupled via Suzuki coupling with diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (126 mg, 0.321 mmol) as described previously to give the desired product in 77 mg (30%). MS: m/e 960.45/962.45 (M+H)⁺, 4.41 min (method 16). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.45 (d, J=2.8 Hz, 1H), 7.75 (dd, J=8.7, 2.6 Hz, 1H), 7.48 (d, J=8.5 Hz, 1H), 5.87 (s, 1H), 5.52 (dd, J=6.4, 1.9 Hz, 1H), 5.14 - 5.01 (m, 2H), 4.68 (d, J=2.3 Hz, 1H), 4.59 (d, J=1.3 Hz, 1H), 4.29 - 4.13 (m, 2H), 2.70 (s, 4H), 2.59 (d, J=2.8 Hz, 4H), 2.44 - 2.06 (m, 2H), 1.91 - 1.74 (m, 2H), 1.72 - 1.34 (m, 19H), 1.30 - 1.21 (m, 16H), 1.15 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H), 0.84

30

(s, 3H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -73.66 (s).

The analogous diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(1,1,1-trifluoro-N-phenylmethylsulfonamido)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate was prepared in a similar fashion using 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide in Step 2 to first give intermediate

(1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(1,1,1-trifluoro-N-phenylmethylsulfonamido)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate which was then carried into the Suzuki coupling as described before. MS: m/e 925.5 ($M+H$)⁺, 2.84 min (method 17). ^1H NMR (400MHz, CHLOROFORM-d) δ 7.48 - 7.38 (m, 3H), 7.37 - 7.28 (m, 1H), 5.87 (s, 1H), 5.52 (dd, $J=6.4$, 1.9 Hz, 1H), 5.14 - 5.01 (m, 2H), 4.71 (d, $J=1.8$ Hz, 1H), 4.60 (d, $J=1.3$ Hz, 1H), 3.89 (br. s., 2H), 2.70 (s, 3H), 2.59 (d, $J=2.5$ Hz, 2H), 2.54 (dd, $J=12.5$, 6.0 Hz, 4H), 2.15 - 2.06 (m, 1H), 1.96 - 1.70 (m, 4H), 1.68 (s, 4H), 1.65 - 1.29 (m, 13H), 1.25 (dd, $J=6.3$, 5.0 Hz, 11H), 1.15 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 0.93 (s, 3H), 0.84 (s, 3H).

Step 4: To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(1,1,1-trifluoro-N-phenylmethylsulfonamido)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (15 mg, 0.016 mmol) in dioxane (2 mL) and MeOH (1 mL) was added 1N NaOH (1 mL, 1 mmol). The mixture was stirred at 50 °C for 3 h. The mixture was neutralized by 1N HCl (1 mL) to pH ~ 6 and solids formed were collected by filtration. The crude product was purified by preparative HPLC using method 14 to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(1,1,1-trifluoro-N-phenylmethylsulfonamido)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

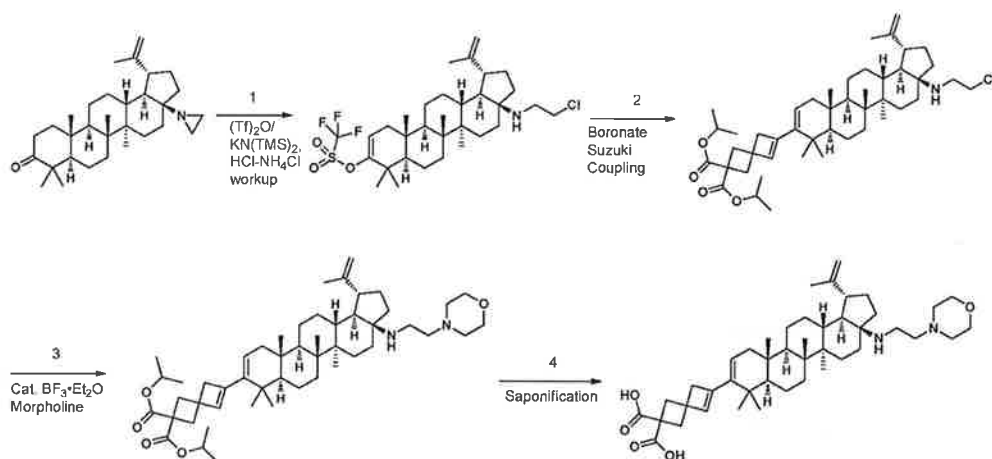
cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid in 42% yield as a solid. MS: m/e 841.5 (M+H)⁺, 2.52 min (method 4). ¹H NMR (400MHz, METHANOL-d₄) δ 7.52 - 7.43 (m, 5H), 5.93 (s, 1H), 5.56 - 5.52 (m, 1H), 4.72 (d, $J=1.8$ Hz, 1H), 4.60 (s, 1H), 3.99 (s., 2H), 2.77 - 2.65 (m, 4H), 2.63 - 2.51 (m, 5H), 2.15 (dd, $J=17.8$, 6.5 Hz, 1H), 1.92 - 1.83 (m, 2H), 1.78-0.94 (m, 19H), 1.69 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H). ¹⁹F NMR (376MHz, METHANOL-d₄) δ -75.37 (s., 3F).

Step 4 for example A3 was carried out in a similar manner: To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(N-(5-chloropyridin-2-yl)-1,1,1-trifluoromethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (32 mg, 0.033 mmol) in dioxane (2 mL) and MeOH (1 mL) was added 1N NaOH (1 mL, 1 mmol). The mixture was stirred at 50 °C for 3 h. The mixture was neutralized by 1N HCl (1 mL) to pH ~ 6 and solids formed were collected by filtration. The crude product was purified by preparative HPLC using method 14 to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(N-(5-chloropyridin-2-yl)-1,1,1-trifluoromethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid in 47% yield as a solid. MS: m/e 876.5 (M+H)⁺, 2.56 min (method 4). ¹H NMR (400MHz, METHANOL-d₄) δ 8.53 (d, $J=2.3$ Hz, 1H), 8.00 (dd, $J=8.7$, 2.6 Hz, 1H), 7.57 (d, $J=8.5$ Hz, 1H), 5.92 (s, 1H), 5.54 (dd, $J=6.4$, 1.9 Hz, 1H), 4.71 (d, $J=1.3$ Hz, 1H), 4.60 (s, 1H), 4.34 - 4.17 (m, 2H), 2.76 - 2.65 (m, 6H), 2.62 - 2.53 (m, 2H), 2.43 - 2.33 (m, 1H), 2.15 (dd, $J=17.9$, 6.7 Hz, 1H), 1.86 (quin, $J=10.6$ Hz, 1H), 1.79-0.94 (m, 20H), 1.68 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H). ¹⁹F NMR (376MHz, METHANOL-d₄) δ -75.55 (s., 3F).

30 Example A4

Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid



5

Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate.

- 10 To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (357 mg, 0.790 mmol) in THF (3 mL) under nitrogen at -78 °C was added trifluoromethanesulfonic anhydride (0.320 mL, 1.9 mmol), followed by a 0.5 M stock solution of potassium bis(trimethylsilyl)amide (1.897 mL, 0.948 mmol) forming a dull
- 15 suspension. Stirring continued for 60 minutes at -78 °C. The reaction was worked up by the addition of 8 mL mixture of 4 mL 1.0 N HCl and 4 mL of a half-saturated ammonium chloride solution. The quenched mixture was stirred at RT for 30 minutes, the organic materials were extracted into ethyl acetate. The crude mixture was separated on a silica gel column eluted with mixture of ethyl acetate in hexanes to furnish 73 mg (15%) of the
- 20 desired product. MS: m/e 620.3/622.3 (M+H)⁺, 3.93 min (method 18). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -74.85.

Step 2: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate.

- (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (73 mg, 0.118 mmol), previously dried, was mixed with diisopropyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (55.4 mg, 0.141 mmol) in a 50 mL RBF fitted with an air condenser and a 3-way stopcock/balloon setup. To this mixture was added sodium carbonate hydrate (43.8 mg, 0.353 mmol),
- tetrakis(triphenylphosphine)palladium (4.08 mg, 3.53 μ mol) and dioxane (2 mL), followed by water (0.5 mL). The mixture was quickly immersed into a dry-ice bath until completely frozen. Standard evacuation/purging cycles were repeated 4 times. Under nitrogen, the frozen solid was allowed to melt at RT, forming a very pale lemon yellow solution. Once the solution became nearly homogeneous, it was immersed into an oil bath at 85 °C. The reaction was allowed to remain at 85 °C for the 2 hours. LCMS analysis showed the desired product, in the forms of water and methanol adducts. The crude reaction mixture was quenched with a mixture of 4 mL saturated ammonium chloride and 4 mL 0.5 N HCl to bring aziridine back to the chloroethyl open form. The desired product was purified by silica gel chromatography eluted with mixture of ethyl acetate and hexanes to give 19 mg (22%). MS: m/e 736.5/738.5 (M+H)⁺, 4.53 min (method 19). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.87 (s, 1H), 5.52 (dd, J=6.5, 2.0 Hz, 1H), 5.07 (dq, J=17.1, 6.3 Hz, 2H), 4.72 (d, J=2.0 Hz, 1H), 4.62 - 4.57 (m, 1H), 3.73 - 3.62 (m, 2H), 2.86 - 2.72 (m, 2H), 2.70 (s, 3H), 2.59 (d, J=2.5 Hz, 2H), 2.17 - 1.82 (m, 4H), 1.80 - 1.70 (m, 3H), 1.69 (s, 3H), 1.66 - 1.28 (m, 18H), 1.25 (dd, J=6.3, 5.0 Hz, 12H), 1.15 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H), 0.82 (s, 3H).

Step 3: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate.

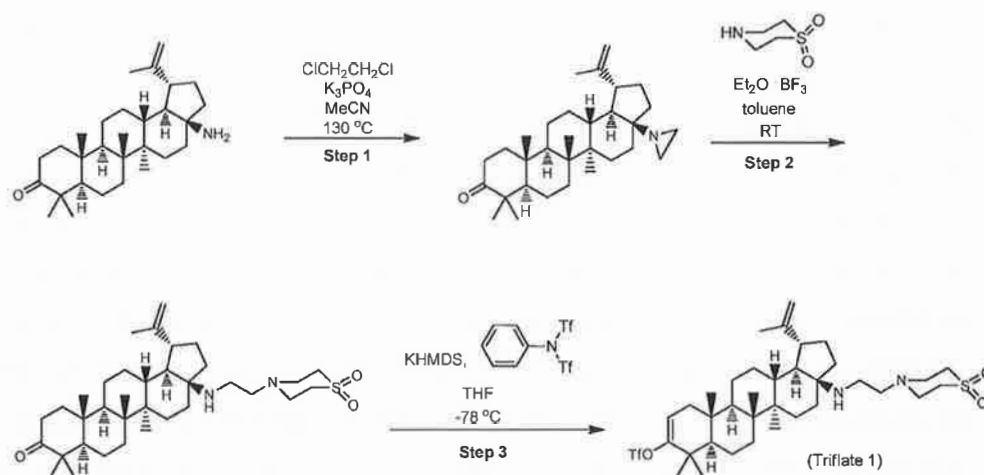
To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (18 mg, 0.024 mmol) in a solution of borontrifluoride etherate in benzene ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ 2% by volume, 2 mL) at RT, was added morpholine (75 μL , 0.857 mmol) forming a cloudy mixture. The mixture was kept at 80 °C for 2 hours. The reaction was diluted with a saturated solution of ammonium chloride in 0.5 N HCl, organic materials were extracted into ethyl acetate (25 mL) three times. The organic extracts were combined and washed with a solution of sodium bicarbonate, the organic materials were concentrated, and purified by silica gel chromatography eluted with mixture of ethyl acetate and hexanes to give 8.1 mg (40%) of the desired product. MS: m/e 787.6 ($\text{M}+\text{H}$)⁺. ¹H NMR (400MHz, CHLOROFORM-d) δ 5.87 (s, 1H), 5.55 - 5.49 (m, 1H), 5.15 - 5.00 (m, 2H), 4.72 (br. s., 1H), 4.59 (br. s., 1H), 3.73 (t, $J=4.4$ Hz, 4H), 2.70 (s, 4H), 2.59 (d, $J=2.3$ Hz, 3H), 2.56 - 2.34 (m, 6H), 2.10 (dd, $J=17.9, 6.7$ Hz, 1H), 1.92 - 1.72 (m, 4H), 1.70 (s, 4H), 1.67 - 1.28 (m, 14H), 1.25 (dd, $J=6.3, 5.0$ Hz, 14H), 1.15 (m, 5H), 1.10 (m, 5H), 1.07 (m, 5H), 0.97 (s, 3H), 0.82 (s, 3H).

Step 4: To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (9 mg, 0.011 mmol) in 1,4-dioxane (1 mL) and MeOH (0.5 mL) was added 1N NaOH (0.5 mL, 0.500 mmol). The mixture was stirred at 50 °C for 3 h. The crude product was purified by Prep HPLC using method 14 to give desired product in 74% yield as a solid. MS: m/e 703.6 ($\text{M}+\text{H}$)⁺, 2.42 min (method 4). ¹H NMR (400MHz, METHANOL-d_4) δ 5.96 (s, 1H), 5.54 (dd, $J=6.1, 1.6$ Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.80 - 3.67 (m, 4H), 3.15 - 3.01 (m, 2H), 2.94 - 2.76 (m, 2H), 2.76 - 2.58 (m, 8H), 2.52 (br. s., 2H), 2.22 - 2.14 (m, 1H), 2.10 - 1.87 (m, 2H), 1.83-1.07 (m, 19H), 1.76 (s, 3H), 1.24 (s, 3H), 1.18 (s, 4H), 1.09 (s, 6H), 0.85 (s, 3H).

Key intermediate: Triflate 1

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate:



Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one

In a pressure vessel, a suspension of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (4.0 g, 9.4 mmol), K_3PO_4 (9.97 g, 47.0 mmol) in 1,2-dichloroethane (300 mL) and acetonitrile (30 mL) was flushed with nitrogen, sealed, and stirred at 130°C overnight. The reaction mixture was cooled to RT, filtered through a bed of silica gel, and rinsed with EtOAc. The filtrate was concentrated *in vacuo* to give crude aziridine (4.0 g, 94%) as a solid which was used for the next step without purification. MS: m/e 452.5 ($\text{M}+\text{H}$)⁺, 2.63 min (method 4).

Step 2: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one

To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (4.0 g, 8.85 mmol) and thiomorpholine 1,1-dioxide (4.79 g, 35.4 mmol) in toluene (30 mL) was added boron trifluoride diethyl etherate (1 mL in 100 mL of toluene, 10 mL) forming a yellow suspension. The mixture was sonicated for 2 min, then stirred at RT for 5 days. The reaction mixture was diluted with EtOAc (200 mL), washed with NaHCO_3 (200 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude

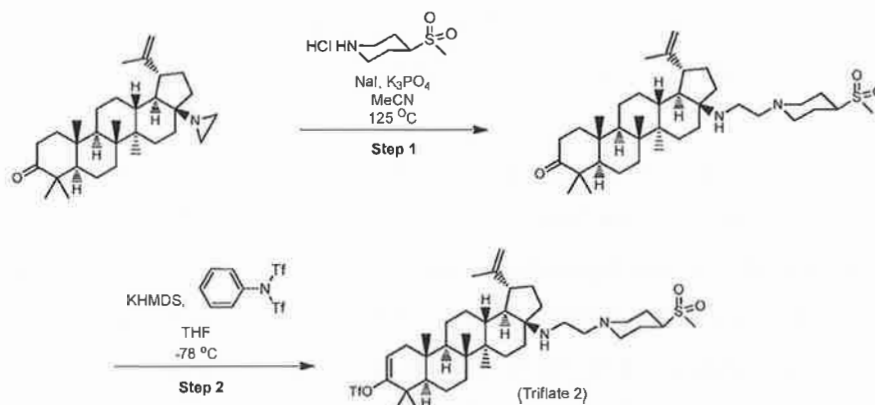
product was purified by a silica gel column (160 gm) eluted with 20-50% of EtOAc/Hexane to give desired ketone (2.95 g, 57%) as a solid. MS: m/e 587.5 (M+H)⁺, 2.39 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.74 - 4.70 (m, 1H), 4.62 - 4.59 (m, 1H), 3.11 - 2.99 (m, 7H), 2.72 - 2.36 (m, H), 1.98 - 0.82 (m, 23H), 1.69 (s, 3H), 1.08 (s, 6H), 1.04 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H).

Step 3: To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (2.95 g, 5.03 mmol) in THF (50 mL) at -78 °C was added KHMDS (1 M in THF, 7.54 mL, 7.54 mmol). The yellow solution was stirred at -78 °C for 30 min. A solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.89 g, 5.28 mmol) in THF (10 mL) was added. The resulted reddish reaction mixture was stirred at -78 °C for 2 h, then warmed to RT and stirred at RT overnight (20 h). The reaction was quenched with saturated aq NH₄Cl (50 mL). The separated aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude product was purified by a silica gel column (160 gm) eluted with 20-80% of EtOAc/Hexane to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (triflate 1) (2.78 g, 77%) as a solid. MS: m/e 719.5 (M+H)⁺, 2.60 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.57 (dd, J=6.8, 2.0 Hz, 1H), 4.76 - 4.71 (m, 1H), 4.64 - 4.61 (m, 1H), 3.13 - 3.02 (m, 7H), 2.85 - 2.75 (m, 1H), 2.73 - 2.64 (m, 2H), 2.62 - 2.52 (m, 2H), 2.17 (dd, J=17.1, 6.8 Hz, 1H), 2.00 - 0.86 (m, 22H), 1.70 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -74.84 (s, 3F).

Key intermediate: Triflate 2

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-

yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate:



5

Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one

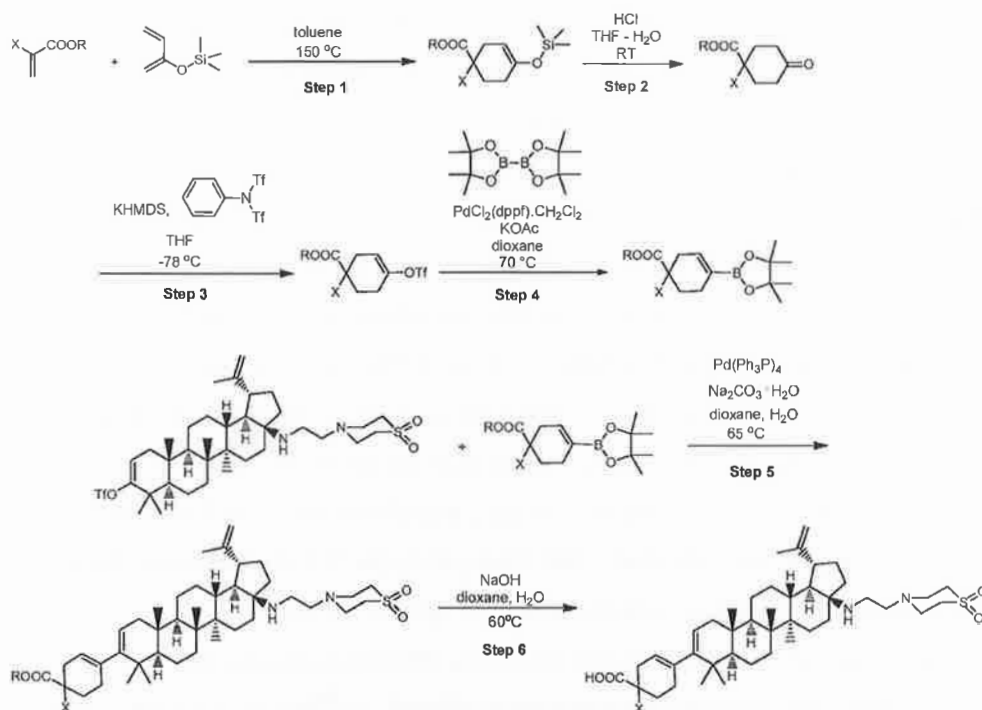
- 10 In a pressure vessel, a suspension of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (5.0 g, 11.07 mmol), 4-(methylsulfonyl)piperidine hydrochloride (4.42 g, 22.14 mmol), NaI (1.659 g, 11.07 mmol) and K₃PO₄ (4.70 g, 22.14 mmol) in toluene (50 mL) and CH₃CN (50 mL) was flushed with nitrogen, sealed, and
- 15 stirred at 125 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between EtOAc (100 mL) and H₂O (100 mL). The separated aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by a silica gel column (240 gm) eluted with 40-80%
- 20 EtOAc/Hexane to give desired ketone (4.26 g, 63%) as a solid. MS: m/e 615.6 (M+H)⁺, 2.40 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.67 (d, J=2.3 Hz, 1H), 4.54 (dd, J=2.3, 1.5 Hz, 1H), 3.07 (dd, J=16.7, 11.7 Hz, 2H), 2.88 - 2.78 (m, 1H), 2.81 (s, 3H), 2.61 - 2.30 (m, 7H), 2.14 - 2.02 (m, 3H), 1.98 - 1.70 (m, 9H), 1.69 - 0.94 (m, 16H), 1.65 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H).

25

Step 2: To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one (4.26 g, 6.93 mmol) in THF (80 mL) at -78 °C was added KHMDS (1 M in THF) (10.39 mL, 10.39 mmol). The resulted orange slurry was stirred at -78 °C for 20 min. A solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (2.72 g, 7.62 mmol) in THF (20 mL) was added. The resulted orange reaction mixture was stirred at -78 °C for 2 h. The reaction was quenched with saturated aq NH₄Cl (100 mL). The separated aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude product was purified by a silica gel column (240 gm), eluted with 40-100% EtOAc/Hexane to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate, (triflate 2) (3.5 g, 68%) as a solid.

MS: m/e 747.4 (M+H)⁺, 2.82 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.56 (dd, J=6.7, 1.9 Hz, 1H), 4.73 (d, J=2.0 Hz, 1H), 4.60 (dd, J=2.1, 1.4 Hz, 1H), 3.17 - 3.07 (m, 2H), 2.88 - 2.79 (m, 1H), 2.85 (s, 3H), 2.69 - 2.54 (m, 3H), 2.52 - 2.42 (m, 2H), 2.19 - 2.07 (m, 4H), 2.03 - 0.88 (m, 24H), 1.69 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -74.85 (s, 3F).

General procedure for the preparation of C-3 α-substituted cyclohexenecarboxylic acid compounds:



Step 1: Preparation of cyclohexenyloxytrimethylsilane

In a pressure vessel, a solution of acrylate (1 eq), (buta-1,3-dien-2-yloxy)trimethylsilane
 5 (1.1 eq) in toluene was flushed with nitrogen, sealed and heated at 150 °C for 1-3 days. The reaction mixture was cooled to RT and concentrated in *vacuo* to give crude product which was used for the next step without purification.

Step 2: Preparation of ketone

10 To a solution of crude product from step 1 (1 eq) in THF was added 0.005 N HCl (0.005 eq). The mixture was stirred at RT overnight. The mixture was extracted with EtOAc, washed with saturated aq NaHCO₃ followed by brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by a silica gel column eluted with 0-50 % of EtOAc/Hexane to give desired ketone.

15

Step 3: Preparation of triflate

To a solution of ketone from Step 2 (1 eq) and 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)-methanesulfonamide (1.1 eq) in THF at -78 °C was added KHMDS (1 M in THF) (1.3 eq). The resulted yellow to orange solution was stirred at -78

°C for 2 h. The reaction was quenched with saturated aq NH₄Cl. The mixture was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by a silica gel column eluted with 0-25 % of EtOAc/Hexane to give desired triflate.

5

Step 4: Preparation of boronate

In a pressure vessel, a mixture of triflate from Step 3 (1 eq), bis(pinacolato)diboron (1.1 eq), KOAc (2.5 eq) and PdCl₂(dppf)-CH₂Cl₂ adduct (0.03 eq) in 1,4-dioxane was flushed with nitrogen, sealed and heated at 70 °C for 2 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by a silica gel column eluted with 0-25 % of EtOAc/Hexane to give desired boronate.

10

Step 5: Suzuki coupling

A mixture of triflate (1 eq), boronate from Step 4 (1eq), Na₂CO₃ H₂O (3 eq) and Pd(Ph₃P)₄ (0.06 eq) in dioxane and H₂O (4 : 1), was flushed with nitrogen, sealed and heated at 65 °C for 2 h, color changed to dark brown. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between EtOAc and H₂O. The separated aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by a silica gel column eluted with 30 - 80% EtOAc/Hexane to give desired ester.

20

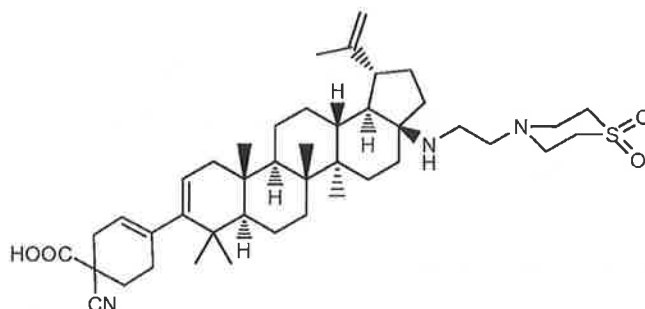
Step 6: Preparation of carboxylic acid

A solution of ester from Step 5 in 1,4-dioxane, MeOH and 1N NaOH (2 : 1 : 1) was stirred at 60 °C for 1-2 h. The reaction mixture was purified by Prep HPLC to give final product.

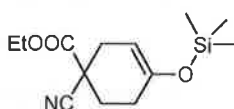
25

Example A5

30 Preparation of 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

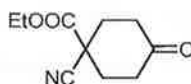


Step 1: Preparation of ethyl 1-cyano-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate



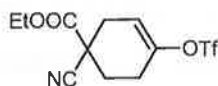
The title compound was prepared following the procedure described in general procedure Step 1, using ethyl 2-cyanoacrylate as reactant and refluxing 1,4-dioxane as the solvent. The crude material was used directly in Step 2.

Step 2: Preparation of ethyl 1-cyano-4-oxocyclohexanecarboxylate



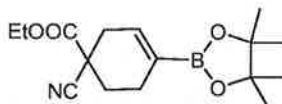
The title compound was prepared in 96% yield as an oil following the procedure described in general procedure Step 2, using ethyl 1-cyano-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate as reactant. MS: m/e 196.15 ($M+H$)⁺, 2.75 min (method 20). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 4.33 (q, $J=7.3$ Hz, 2H), 2.76 - 2.66 (m, 2H), 2.59 - 2.44 (m, 4H), 2.36 - 2.27 (m, 2H), 1.37 (t, $J=7.2$ Hz, 3H).

Step 3: Preparation of ethyl 1-cyano-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate



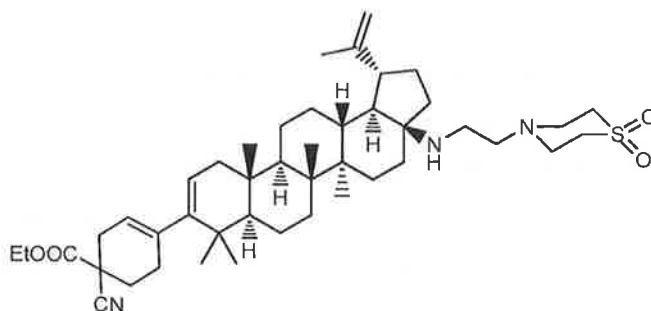
The title compound was prepared in 64% yield as an oil following the procedure described in general procedure Step 3, using ethyl 1-cyano-4-oxocyclohexanecarboxylate as the reactant. ¹H NMR (400MHz, CHLOROFORM-d) δ 5.81 (ddt, *J*=4.6, 3.1, 1.6 Hz, 1H), 4.32 (q, *J*=7.0 Hz, 2H), 2.93 - 2.85 (m, 1H), 2.80 - 2.67 (m, 2H), 2.58 - 2.48 (m, 1H), 2.40 - 2.33 (m, 1H), 2.31 - 2.22 (m, 1H), 1.36 (t, *J*=7.2 Hz, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -73.61 (s, 3F).

Step 4: Preparation of ethyl 1-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate



The title compound was prepared in 97% yield as an oil following the procedure described in general procedure Step 4, using ethyl 1-cyano-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate as reactant. ¹H NMR (400MHz, CHLOROFORM-d) δ 6.50 - 6.46 (m, 1H), 4.29 (q, *J*=7.0 Hz, 2H), 2.78 - 2.58 (m, 2H), 2.52 - 2.32 (m, 2H), 2.24 - 2.17 (m, 1H), 1.95 (ddd, *J*=13.2, 10.8, 5.6 Hz, 1H), 1.34 (t, *J*=7.2 Hz, 3H), 1.27 (s, 12H)

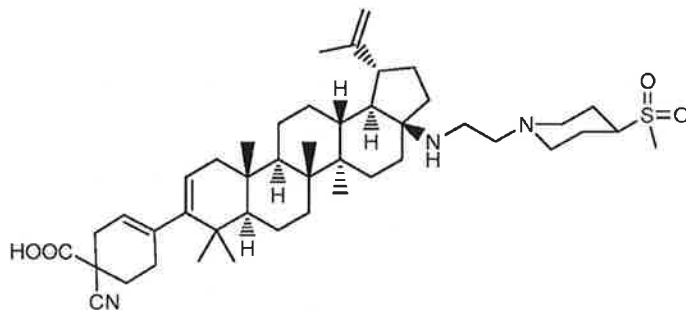
Step 5: Preparation of ethyl 1-cyano-4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate



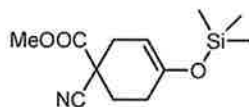
- The title compound was prepared following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and ethyl 1-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as reactants. The product was isolated as a mixture of diastereoisomers (solid, 61% yield). MS: m/e 748.6 (M+H)⁺, 2.99 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.35 (d, J=1.8 Hz, 1H), 5.28 - 5.23 (m, 1H), 4.73 (d, J=1.8 Hz, 1H), 4.61 (s, 1H), 4.29 (q, J=7.0 Hz, 2H), 3.13 - 3.01 (m, 8H), 2.80 - 2.46 (m, 9H), 2.33 - 2.15 (m, 2H), 2.08 - 0.82 (m, 22H), 1.70 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.07 (s, 3H), 0.97 (s, 3H), 1.03 - 0.92 (m, 6H), 0.86 (s, 3H).
- Step 6:** 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using ethyl 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as reactant. The title compound was isolated as a mixture of diastereomers (solid, 84% yield). MS: m/e 720.6 (M+H)⁺, 2.82 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.35 (s., 1H), 5.24 (s., 1H), 4.78 (s., 1H), 4.66 (s, 1H), 3.23 - 2.40 (m, 13H), 2.29 - 0.81 (m, 34H), 1.70 (s, 3H), 1.14 (s, 3H), 1.01 (s., 3H), 0.88 (s, 3H).

Example A6

Preparation of 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

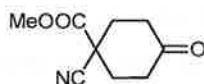


Step 1: Preparation of methyl 1-cyano-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate



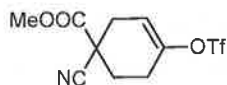
The title compound was prepared following the procedure described in general procedure Step 1, using methyl 2-cyanoacrylate as reactant and 1,4-dioxane as solvent at 90 °C.

Step 2: Preparation of methyl 1-cyano-4-oxocyclohexanecarboxylate



The title compound was prepared as following the procedure described in general procedure Step 2, using methyl 1-cyano-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate as reactant. The crude material was isolated as an oil. ¹H NMR (400MHz, CHLOROFORM-d) δ 3.90 (s, 3H), 2.76 - 2.65 (m, 2H), 2.59 - 2.44 (m, 4H), 2.38 - 2.26 (m, 2H).

Step 3: Preparation of methyl 1-cyano-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate



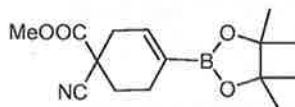
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The title compound was prepared following the procedure described in general procedure Step 3, using methyl 1-cyano-4-oxocyclohexanecarboxylate as reactant. The product was isolated as an oil in 51% yield. ^1H NMR (400MHz, CHLOROFORM- d) δ 5.81 (qd, $J=3.1, 2.0$ Hz, 1H), 3.88 (s, 3H), 2.94 - 2.84 (m, 1H), 2.82 - 2.67 (m, 2H), 2.59 - 2.47 (m, 1H), 2.42 - 2.33 (m, 1H), 2.31 - 2.22 (m, 1H). ^{19}F NMR (376MHz, CHLOROFORM- d) δ -73.62 (s, 3F).

10

Step 4: Preparation of methyl 1-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate

15

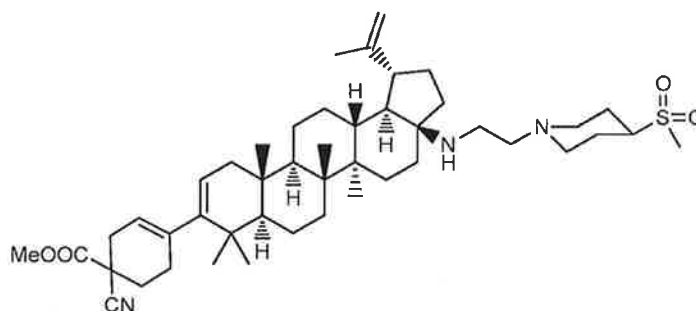


The title compound was prepared following the procedure described in general procedure Step 4, using methyl 1-cyano-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate as reactant. The product was obtained in 62% yield as an oil. ^1H NMR (400MHz, CHLOROFORM- d) δ 6.51 - 6.46 (m, 1H), 3.85 (s, 3H), 2.78 - 2.59 (m, 2H), 2.52 - 2.33 (m, 2H), 2.25 - 2.17 (m, 1H), 1.96 (ddd, $J=13.1, 10.8, 5.8$ Hz, 1H), 1.27 (s, 12H).

20

Step 5: Preparation of methyl 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

30

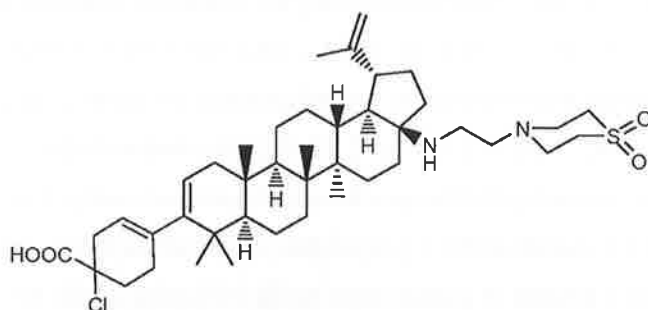


- The title compound was prepared following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 1-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as reactants. The product was isolated as a mixture of diastereomers (solid, 61% yield). MS: m/e 762.6 (M+H)⁺, 3.01 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.34 (d, J=2.0 Hz, 1H), 5.28 - 5.22 (m, 1H), 4.71 (d, J=2.0 Hz, 1H), 4.60 - 4.57 (m, 1H), 3.85 (s, 3H), 3.17 - 3.06 (m, 3H), 2.87 - 2.78 (m, 2H), 2.84 (s, 3H), 2.74 - 2.40 (m, 10H), 2.33 - 0.78 (m, 27H), 1.69 (s, 3H), 1.07 (s, 3H), 1.01 - 0.93 (m, 6H), 0.96 (s, 3H), 0.85 (s, 3H).
- Step 6:** 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using methyl 1-cyano-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as reactant. The product was isolated as a mixture of diastereomers (solid, 50% yield). MS: m/e 748.6 (M+H)⁺, 2.97 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.36 (s, 1H), 5.24 (d, J=5.5 Hz, 1H), 4.80 (s, 1H), 4.67 (s, 1H), 3.31 - 3.13 (m, 3H), 3.12 - 2.89 (m, 6H), 2.86 (s, 3H),

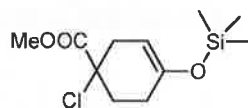
2.78 - 2.45 (m, 5H), 2.33 - 0.85 (m, 29H), 1.70 (s, 3H), 1.17 (s, 3H), 1.02 - 0.94 (m, 6H), 1.00 (s, 3H), 0.87 (s, 3H).

Example A7

- 5 **Preparation of 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid**

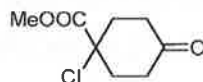


- 10 **Step 1: Preparation of methyl 1-chloro-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate**



- 15 The title compound was prepared following the procedure described in general procedure Step 1, using methyl 2-chloroacrylate as reactant.

Step 2: Preparation of methyl 1-chloro-4-oxocyclohexanecarboxylate

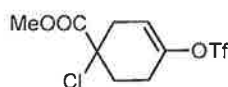


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The title compound was prepared following the procedure described in general procedure Step 2, using methyl 1-chloro-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate. The product was isolated as an oil in 46% yield. MS: m/e 191.1 ($M+H$)⁺, 2.95 min (method 6).

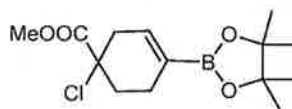
^1H NMR (500MHz, CHLOROFORM- d) δ 3.86 (s, 3H), 2.80 - 2.71 (m, 2H), 2.55 - 2.39 (m, 6H).

Step 3: Preparation of methyl 1-chloro-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate



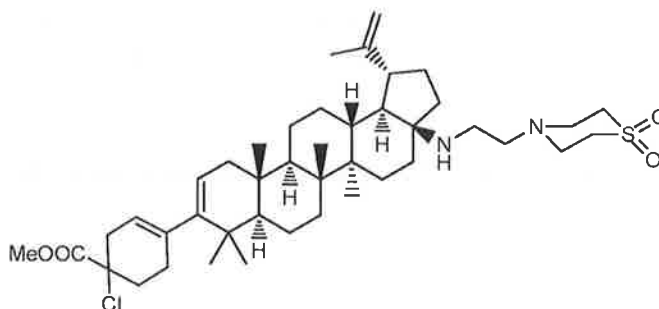
The title compound was prepared following the procedure described in general procedure Step 3, using methyl 1-chloro-4-oxocyclohexanecarboxylate as reactant. The product was isolated as an oil in 47% yield. ^1H NMR (400MHz, CHLOROFORM- d) δ 5.74 - 5.70 (m, 1H), 3.84 (s, 3H), 3.07 - 2.99 (m, 1H), 2.83 - 2.65 (m, 2H), 2.53 - 2.29 (m, 3H).

Step 4: Preparation of methyl 1-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate



The title compound was prepared following the procedure described in general procedure Step 4, using methyl 1-chloro-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate as reactant. The product was isolated as an oil in 28% yield. ^1H NMR (400MHz, CHLOROFORM- d) δ 6.45 - 6.41 (m, 1H), 3.81 (s, 3H), 3.00 - 2.91 (m, 1H), 2.71 - 2.63 (m, 1H), 2.50 - 2.10 (m, 4H), 1.27 (s, 12H).

Step 5: Preparation of methyl 1-chloro-4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

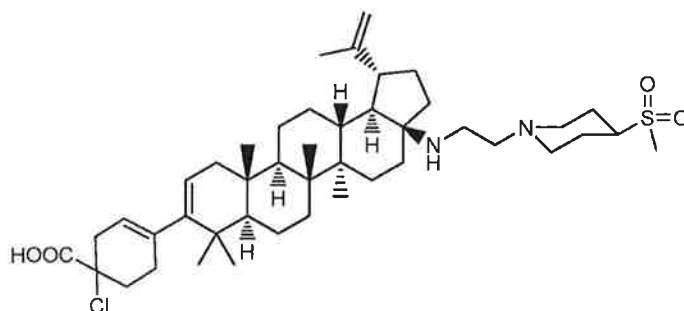


The title compound was prepared following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 1-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as reactants. The product was isolated as a mixture of diastereoisomers. MS: m/e 743.5 (M+H)⁺, 3.01 min (method 4).

Step 6: 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using methyl 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as reactant. The product was isolated as a mixture of diastereomers (solid, 10% yield). MS: m/e 729.5 (M+H)⁺, 2.96 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.28 (s, 1H), 5.21 (d, J=4.3 Hz, 1H), 4.75 (s, 1H), 4.63 (s, 1H), 3.16 - 0.68 (m, 41H), 1.70 (s, 3H), 1.13 (s, 3H), 1.00 (s, 3H), 1.00 - 0.94 (m, 6H), 0.87 (s, 3H).

Example A8

Preparation of 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

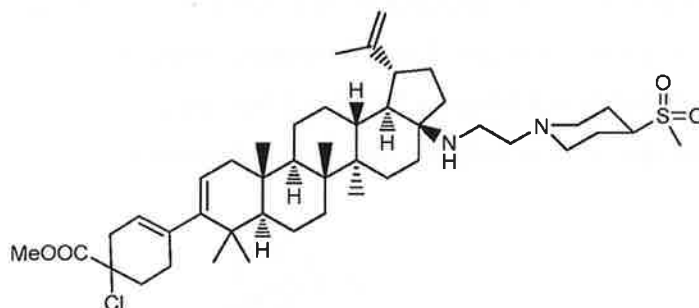


5

Step 1 - Step 4 - Same as described in example A7.

Step 5: Preparation of methyl 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate

10



15

The title compound was prepared following the method described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 1-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as reactants. The product

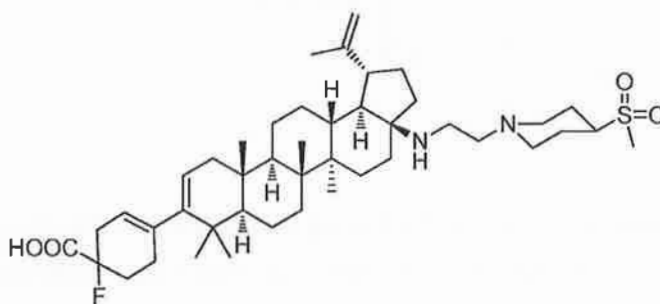
20

was isolated as a mixture of diastereomers, which was used in next step without purification. MS: m/e 771.5 ($M+H$)⁺, 3.06 min (method 4).

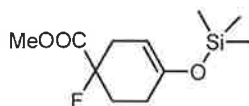
Step 6: 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using methyl 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as reactant. The product was isolated as a mixture of diastereomers (solid, 7% yield). MS: m/e 757.5 ($M+H$)⁺, 2.90 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.31 (s, 1H), 5.24 (d, $J=5.0$ Hz, 1H), 4.78 (s, 1H), 4.65 (s, 1H), 3.35 - 2.40 (m, 14H), 2.87 (s, 3H), 2.32 - 0.82 (m, 28H), 1.71 (s, 3H), 1.17 (s, 3H), 1.01 (s, 6H), 0.97 - 0.95 (m, 3H), 0.88 (s, 3H).

Example A9

Preparation of 1-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

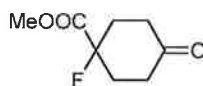


Step 1: Preparation of methyl 1-fluoro-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate



The title compound was prepared following the procedure described in general procedure Step 1, using methyl 2-fluoroacrylate as reactant and taken to the next step without
5 further purification.

Step 2: Preparation of methyl 1-fluoro-4-oxocyclohexanecarboxylate



10

The title compound was prepared following the procedure described in general procedure Step 2, using methyl 1-fluoro-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate as reactant. The product was isolated as an oil in 34% yield. MS: m/e 175.1 ($M+H$)⁺, 2.04 min (method 6). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 3.77 (s, 3H), 2.68 - 2.56 (m, 2H), 2.40 - 2.15 (m, 6H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -168.02 (s, 1F).
15

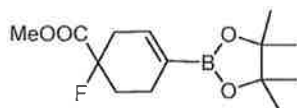
Step 3: Preparation of methyl 1-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate



20

The title compound was prepared following the procedure described in general procedure Step 3, using methyl 1-fluoro-4-oxocyclohexanecarboxylate as reactant. The product was isolated as an oil in 16% yield. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 5.74 - 5.70 (m, 1H), 3.85 (s, 3H), 2.94 - 2.77 (m, 1H), 2.73 - 2.57 (m, 2H), 2.47 - 2.38 (m, 1H), 2.35 - 2.10 (m, 2H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -73.77 (s, 3F), -163.80 (s, 1F).
25

Step 4: Preparation of methyl 1-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate



The title compound was prepared following the procedure described in general procedure

- 5 Step 4, using methyl 1-chloro-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate as reactant. The product was isolated as an oil,. ^1H NMR (400MHz, CHLOROFORM-d) δ 6.48 - 6.44 (m, 1H), 3.81 (s, 3H), 2.81 - 2.64 (m, 1H), 2.55 - 2.42 (m, 1H), 2.37 - 2.28 (m, 2H), 2.15 - 2.07 (m, 1H), 2.01 - 1.82 (m, 1H), 1.27 (s, 12H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -161.94 (s, 1F)

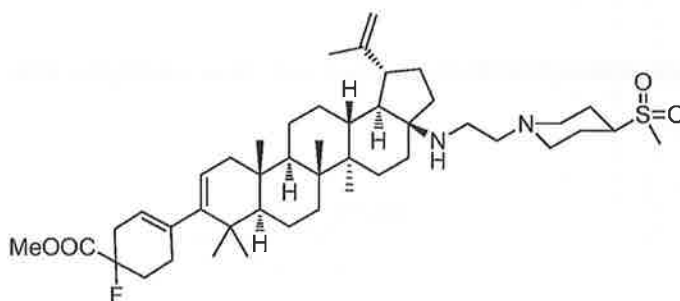
10

Step 5: Preparation of methyl 1-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

- 15 **cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate**



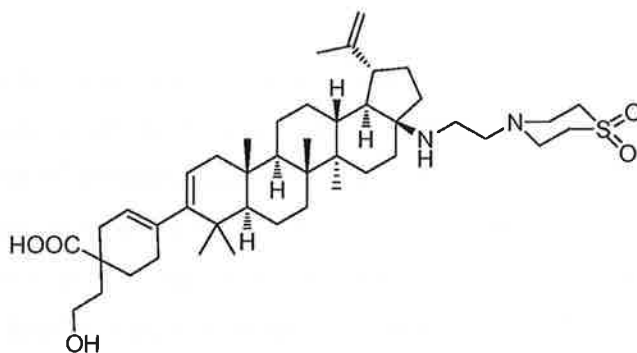
The title compound was prepared following the procedure described in general procedure

- 20 Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 1-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as reactants. The product
- 25 was isolated as a mixture of diastereomers, which was used in next step without further purification. MS: m/e 755.5 (M+H) $^+$, 2.94 min (method 4).

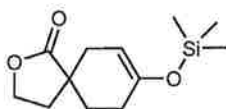
- Step 6:** 1-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using methyl 1-chloro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as reactant. The product was isolated as a mixture of diastereomers (solid, 23% yield). MS: m/e 741.6 (M+H)⁺, 2.77 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.30 (s, 1H), 5.23 (d, $J=4.5$ Hz, 1H), 4.76 (s, 1H), 4.64 (s, 1H), 3.24 - 2.73 (m, 6H), 2.85 (s, 3H), 2.61 - 0.80 (m, 36H), 1.69 (s, 3H), 1.14 (s, 3H), 1.00 (s, 3H), 1.00 - 0.92 (m, 6H), 0.86 (s, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -157.26 - -158.46 (m, 1F).

Example A10

- Preparation of 1-(2-hydroxyethyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid**

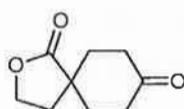


Step 1: Preparation of 8-((trimethylsilyl)oxy)-2-oxaspiro[4.5]dec-7-en-1-one



The title compound was prepared following the procedure described in general procedure Step 1, using 3-methylenedihydrofuran-2(3H)-one as reactant.

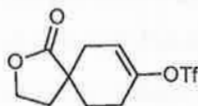
5 Step 2: Preparation of 2-oxaspiro[4.5]decane-1,8-dione



The title compound was prepared following the procedure described in general procedure Step 2, using 8-((trimethylsilyl)oxy)-2-oxaspiro[4.5]dec-7-en-1-one as reactant. The product was isolated as a solid in 48% yield. MS: m/e 169.1 ($M+H$)⁺, 1.43 min (method 6). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 4.38 (t, $J=7.0$ Hz, 2H), 2.77 (ddd, $J=15.0$, 8.1, 5.8 Hz, 2H), 2.40 - 2.31 (m, 2H), 2.31 (t, $J=7.0$ Hz, 2H), 2.26 - 2.18 (m, 2H), 1.99 - 1.91 (m, 2H).

15

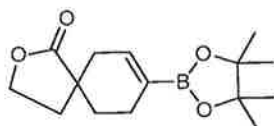
Step 3: Preparation of 1-oxo-2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate



The title compound was prepared following the procedure described in general procedure Step 3, using 2-oxaspiro[4.5]decane-1,8-dione as reactant. The product was isolated as an oil in 83% yield. MS: m/e 301.1 ($M+H$)⁺, 3.81 min (method 6). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 5.80 (dt, $J=5.7$, 2.8 Hz, 1H), 4.42 - 4.30 (m, 2H), 2.65 - 2.57 (m, 1H), 2.57 - 2.38 (m, 2H), 2.27 - 2.14 (m, 3H), 2.09 (ddd, $J=13.6$, 10.5, 6.5 Hz, 1H), 1.84 (ddt, $J=13.5$, 5.6, 2.7 Hz, 1H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -73.83 (s, 3F).

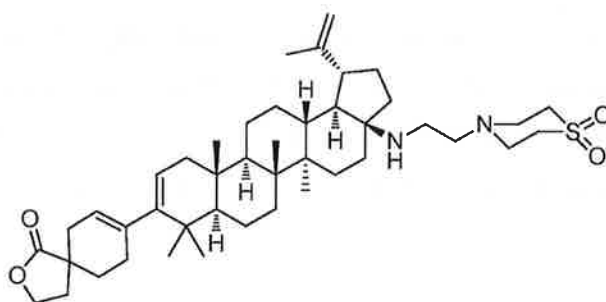
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Step 4: Preparation of 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-oxaspiro[4.5]dec-7-en-1-one



The title compound was prepared following the procedure described in general procedure Step 4, using methyl 1-oxo-2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate as
 5 reactant. The product was isolated as a solid in 52% yield. ^1H NMR (400MHz, CHLOROFORM- d) δ 6.53 (dd, $J=4.6, 2.1$ Hz, 1H), 4.35 - 4.23 (m, 2H), 2.53 - 2.33 (m, 2H), 2.18 - 2.02 (m, 4H), 1.83 (ddd, $J=13.1, 11.6, 5.6$ Hz, 1H), 1.69 - 1.62 (m, 1H), 1.32 - 1.23 (m, 12H).

- 10 **Step 5: Preparation of 8-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-oxaspiro[4.5]dec-7-en-1-one**



The title compound was prepared following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-oxaspiro[4.5]dec-7-en-1-one as reactants and 85°C. The product was obtained as a mixture of diastereoisomers and was used without further purification in the next step. MS: m/e 721 ($M+H$) $^+$, 2.72 min (method 4).

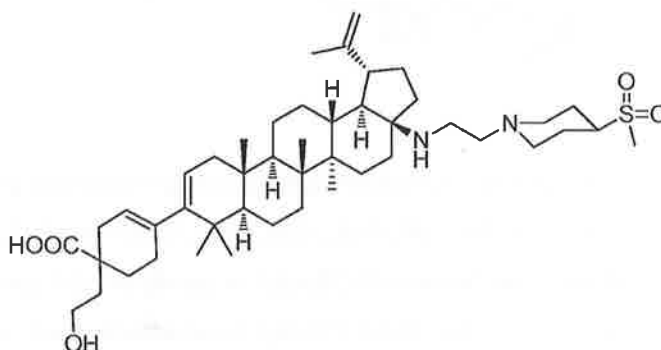
Step 6: 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(2-hydroxyethyl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using 8-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-oxaspiro[4.5]dec-7-en-1-one as reactant. The product was obtained as a mixture of diastereomers (solid, 13%). MS: m/e 739.5 (M+H)⁺, 2.64 min (method 4). ¹H NMR (400MHz, METHANOL-d₄) δ 5.30 (s, 1H), 5.18 (d, J=4.5 Hz, 1H), 4.72 (s, 1H), 4.62 (s, 1H), 3.65 - 3.57 (m, 2H), 3.18 - 3.00 (m, 8H), 2.79 - 2.64 (m, 4H), 2.60 - 2.50 (m, 2H), 2.37 - 0.83 (29H), 1.71 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H), 0.98 - 0.94 (m, 6H), 0.90 (s, 3H).

15

Example A11

Preparation of 1-(2-hydroxyethyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

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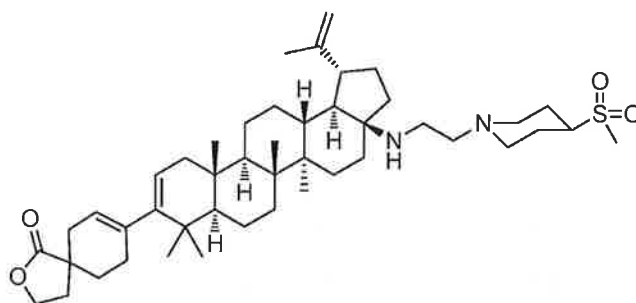


Step 1 - Step 4 - Same as described in example A10.

Step 5: Preparation of 8-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-

25

(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-oxaspiro[4.5]dec-7-en-1-one



5

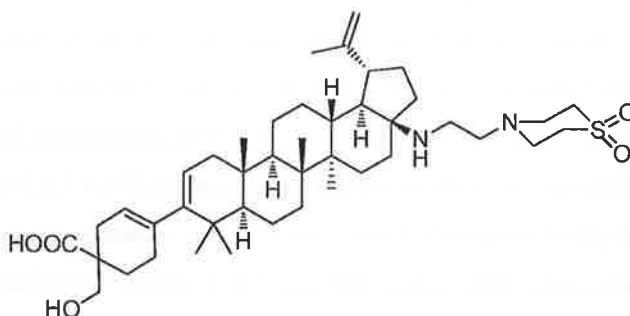
The title compound was prepared following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-oxaspiro[4.5]dec-7-en-1-one as reactants. The product was isolated as diastereomers (solid, 59% yield). MS: m/e 749.7 (M+H)⁺, 4.10 min (method 7). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.35 (d, J=2.8 Hz, 1H), 5.24 - 5.19 (m, 1H), 4.72 (d, J=2.0 Hz, 1H), 4.59 (dd, J=2.3, 1.5 Hz, 1H), 4.37 - 4.25 (m, 2H), 3.12 (dd, J=14.6, 12.0 Hz, 2H), 2.87 - 2.78 (m, 1H), 2.84 (s, 3H), 2.67 - 2.53 (m, 3H), 2.50 - 2.40 (m, 3H), 2.33 - 0.90 (m, 35H), 1.70 (s, 3H), 1.09 (s, 3H), 0.98 - 0.92 (m, 6H), 0.96 (s, 3H), 0.86 (s, 3H).

Step 6: 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(2-hydroxyethyl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using 8-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-oxaspiro[4.5]dec-7-en-1-one as reactant. The product was

isolated as a mixture of diastereomers (solid, 51% yield). MS: m/e 767.6 ($M+H$)⁺, 2.35 min (method 4). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 5.32 (s, 1H), 5.17 (d, $J=5.5$ Hz, 1H), 4.73 (s, 1H), 4.61 (s, 1H), 3.78 - 3.72 (m, 2H), 3.20-3.12 (m, 2H), 2.89 - 2.80 (m, 1H), 2.85 (s, 3H), 2.78 - 2.45 (m, 6H), 2.27 - 0.92(m, 35H), 1.69 (s, 3H), 1.11 (s, 3H),
 5 0.97 (s, 3H), 0.95 - 0.90 (m, 6H), 0.86 (s, 3H).

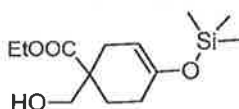
Example A12

**Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 10 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(hydroxymethyl)cyclohex-3-enecarboxylic acid**



Step 1: Preparation of ethyl 1-(hydroxymethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate

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The title compound was prepared following the procedure described in general procedure Step 1, using ethyl 2-(hydroxymethyl)acrylate as reactant.

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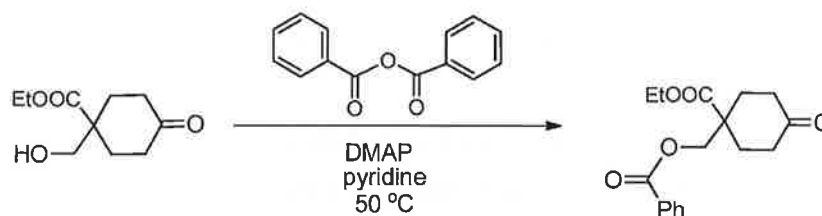
Step 2

a: Preparation of ethyl 1-(hydroxymethyl)-4-oxocyclohexanecarboxylate



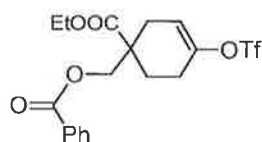
The title compound was prepared following the procedure described in general procedure Step 2, using ethyl 1-(hydroxymethyl)-4-((trimethylsilyl)oxy)cyclohex-3-enecarboxylate as reactant. The product was isolated as a solid in 39% yield. MS: m/e 201.1 ($M+H$)⁺, 1.40 min (method 2). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 4.28 (q, $J=7.0$ Hz, 2H), 3.74 (d, $J=6.3$ Hz, 2H), 2.54 - 2.33 (m, 6H), 2.08 (t, $J=6.4$ Hz, 1H), 1.83 - 1.72 (m, 2H), 1.32 (t, $J=7.2$ Hz, 3H).

b: Preparation of (1-(ethoxycarbonyl)-4-oxocyclohexyl)methyl benzoate



To a solution of ethyl 1-(hydroxymethyl)-4-oxocyclohexanecarboxylate from Step 2a (200 mg, 1 mmol) in pyridine (5 mL) was added DMAP (24.4 mg, 0.2 mmol). The mixture was heated to 50 °C and benzoic anhydride (249 mg, 1.1 mmol) was added. The reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was concentrated in *vacuo*. The residue was dissolved in CH₂Cl₂ (10 mL), washed with NaHCO₃ (10 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude product was purified by a silica gel column eluted with 20% EtOAc/Hexane to give desired product (288 mg, 95%) as an oil. MS: m/e 305.1 ($M+H$)⁺, 3.75 min (method 6). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.03 - 7.99 (m, 2H), 7.62 - 7.56 (m, 1H), 7.49 - 7.43 (m, 2H), 4.45 (s, 2H), 4.28 (q, $J=7.0$ Hz, 2H), 2.61 - 2.38 (m, 6H), 1.90 - 1.80 (m, 2H), 1.28 (t, $J=7.0$ Hz, 3H).

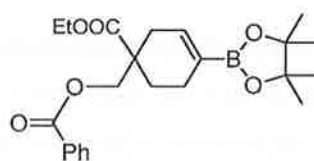
Step 3: Preparation of (1-(ethoxycarbonyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)methyl benzoate



The title compound was prepared following the procedure described in general procedure Step 3, using (1-(ethoxycarbonyl)-4-oxocyclohexyl)methyl benzoate as reactant. The product was isolated as an oil in 89% yield. MS: m/e 437.2 ($M+H$)⁺, 4.30 min (method 6). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.03 - 7.98 (m, 2H), 7.62 - 7.56 (m, 1H), 7.48 - 7.42 (m, 2H), 5.79 (td, $J=3.3$, 1.8 Hz, 1H), 4.47 - 4.38 (m, 2H), 4.21 (qd, $J=7.2$, 2.1 Hz, 2H), 2.91 - 2.83 (m, 1H), 2.58 - 2.27 (m, 4H), 1.94 (ddd, $J=13.4$, 8.5, 6.4 Hz, 1H), 1.24 (t, $J=7.0$ Hz, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -73.84 (s, 3F).

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Step 4: Preparation of (1-(ethoxycarbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)methyl benzoate

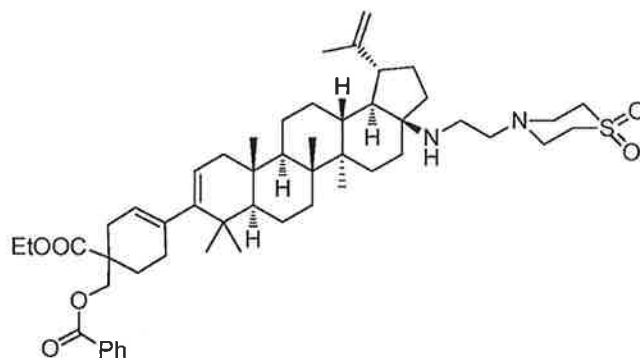


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The title compound was prepared following the procedure described in general procedure Step 4, using (1-(ethoxycarbonyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)methyl benzoate as reactant. The product was isolated as an oil in 90% yield. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.00 (dd, $J=8.3$, 1.3 Hz, 2H), 7.59 - 7.54 (m, 1H), 7.44 (d, $J=8.0$ Hz, 2H), 6.56 - 6.52 (m, 1H), 4.45 - 4.36 (m, 2H), 4.17 (q, $J=7.0$ Hz, 2H), 2.76 - 2.68 (m, 1H), 2.28 - 2.19 (m, 3H), 2.04 - 1.96 (m, 1H), 1.91 - 1.83 (m, 1H), 1.27 (s, 12H), 1.21 (t, $J=7.2$ Hz, 3H).

Step 5: Preparation of (4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(ethoxycarbonyl)cyclohex-3-en-1-yl)methyl benzoate

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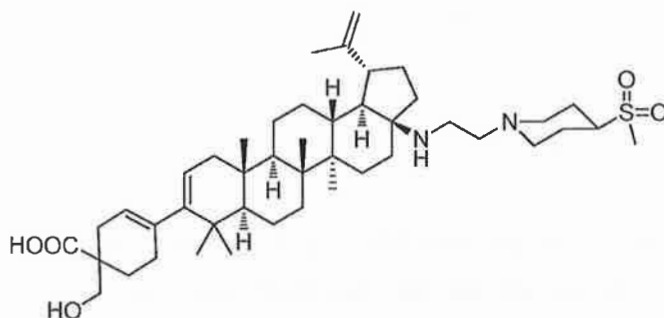


The title compound was prepared following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and (1-(ethoxycarbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)methyl benzoate as reactants at 85 °C. The product was obtained as a mixture of diastereomers, which was used in next step without purification,. MS: m/e 857.6 (M+H)⁺, 2.97 min (method 4).

Step 6: 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(hydroxymethyl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using (4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-1-(ethoxycarbonyl)cyclohex-3-en-1-yl)methyl benzoate as reactant. The product was obtained as a mixture of diastereomers (solid, 10%). MS: m/e 725.6 (M+H)⁺, 2.61 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.30 (s, 1H), 5.17 (s, 1H), 4.72 (s, 1H), 4.60 (s, 1H), 3.11 - 3.04 (m, 2H), 2.78 - 0.83 (m, 41H) 1.70 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H), 0.97 - 0.90 (m, 6H), 0.85 (s, 3H).

Example A13

Preparation of 1-(hydroxymethyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid

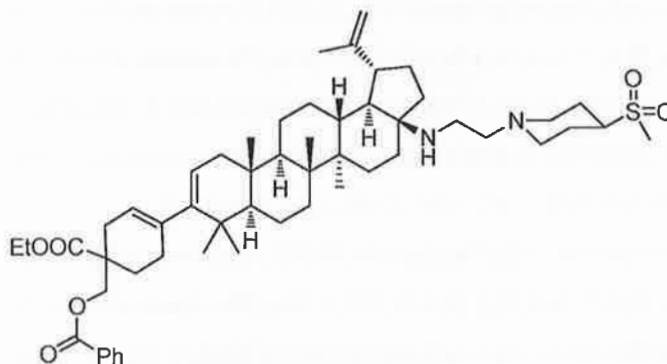


5

Step 1 - Step 4 - Same as described in example A12.

Step 5: Preparation of (1-(ethoxycarbonyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)methyl benzoate

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The title compound was prepared as following the procedure described in general procedure Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and (1-(ethoxycarbonyl)-4-(4,4,5,5-

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tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)methyl benzoate as reactants.

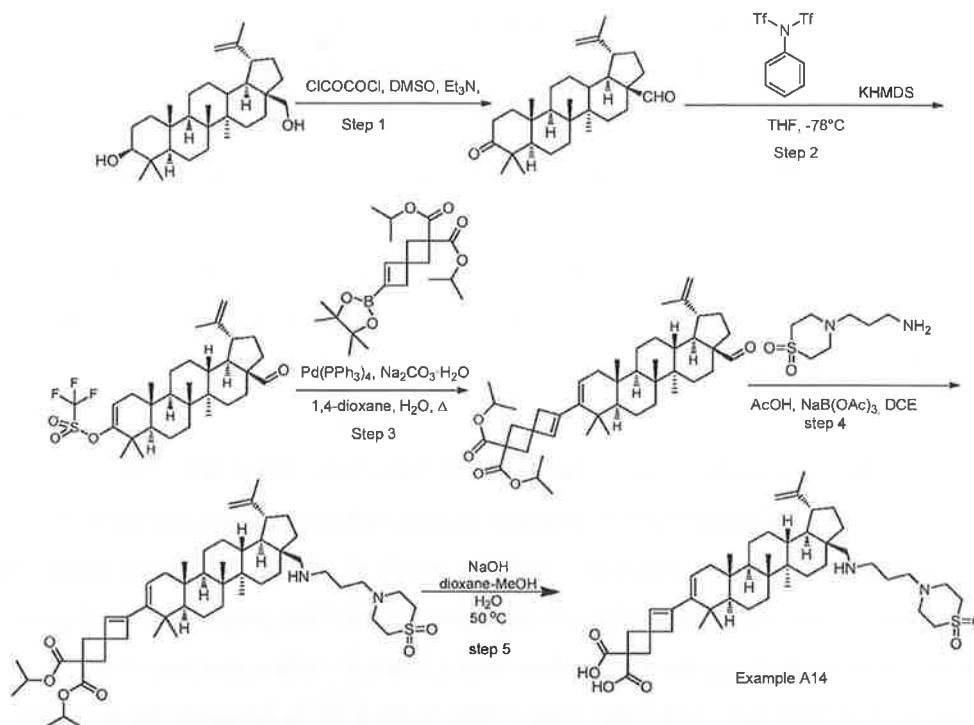
The product was obtained as a mixture of diastereomers. MS: m/e 885.6 (M+H)⁺, 2.80 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.01 (dd, J=8.3, 1.3 Hz, 2H), 7.58 - 7.52 (m, 1H), 7.46 - 7.40 (m, 2H), 5.35 (s, 1H), 5.19 (d, J=5.8 Hz, 1H), 4.71 (d, J=1.8 Hz, 1H), 4.58 (s, 1H), 4.49 - 4.38 (m, 2H), 4.21 - 4.14 (m, 2H), 3.11 (t, J=12.3 Hz, 2H), 2.87 - 2.77 (m, 1H), 2.83 (s, 3H), 2.72 - 2.53 (m, 4H), 2.51 - 2.41 (m, 2H), 2.27 - 0.78 (m, 33H), 1.69 (s, 3H), 1.22 (t, J=7.0 Hz, 3H), 1.07 (s, 3H), 0.96 (s, 3H), 0.97 - 0.90 (m, 6H), 0.85 (s, 3H).

- 10 **Step 6:** 1-(hydroxymethyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the procedure described in general procedure Step 6, using (1-(ethoxycarbonyl)-4-
- 15 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)methyl benzoate as reactant. The product was obtained as a mixture of diastereomers (solid, 47%). MS: m/e 753.5 (M+H)⁺, 2.32
- 20 min (method 4). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.31 (s, 1H), 5.18 (s, 1H), 4.74 (s, 1H), 4.63 (s, 1H), 3.65 (s, 2H), 3.17 (t, J=11.3 Hz, 2H), 2.93 - 2.66 (m, 5H), 2.85 (s, 3H), 2.62 - 2.49 (m, 2H), 2.27 - 0.82 (m, 33H), 1.69 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.97 - 0.90 (m, 6H), 0.86 (s, 3H).

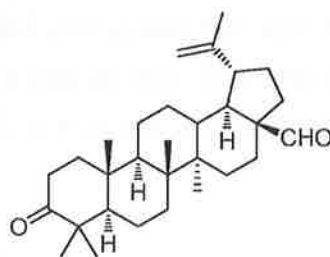
25 Example A14

Preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid

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Step 1: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carbaldehyde



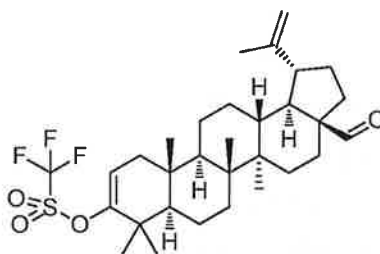
To a 2M solution of oxalyl chloride (47.0 mL, 94 mmol) in CH_2Cl_2 , was added a solution of DMSO (13.7 mL, 192 mmol) in CH_2Cl_2 (20 mL) dropwise at -15°C . After 5 min, a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13bR)-3a-(hydroxymethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (4.43 g, 10.01 mmol) in a mixture of DMSO (30 mL) and CH_2Cl_2 (50 mL) was added at -15°C . Triethylamine (56 mL) was added 15 minutes later and the stirring was continued for another 10 min. The reaction mixture was allowed to warm up to RT. The reaction was quenched by addition of water (100 mL), and the reaction

mixture was extracted with CH_2Cl_2 (70 mL X 3). The combined organic layers were washed with brine (30 mL X 3), dried over MgSO_4 , filtered and concentrated. The crude material was purified using silica gel chromatography eluted with a mixture of ethyl acetate and hexanes, to give the product as a solid (3.3g 75%). LCMS: m/e 461.15 ($\text{M}+\text{Na}$)⁺, 2.91 min (method 2).

5

Step 2: Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-formyl-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

10



The title compound was prepared following the procedure described in method 1 for the preparation of intermediate 1, Step 5, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13bR)-

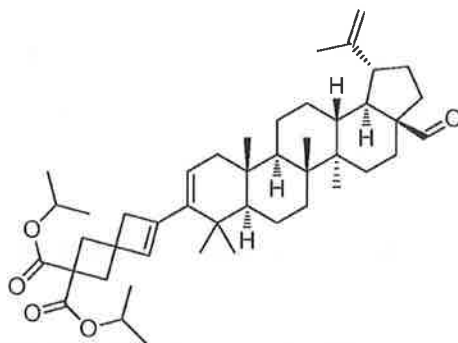
15 5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carbaldehyde as the starting material. (71% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 9.69 (d, $J=1.8$ Hz, 1H), 5.58 (dd, $J=6.7, 2.1$ Hz, 1H), 4.89 - 4.54 (m, 2H), 2.90 (td, $J=11.0, 5.8$ Hz, 1H), 2.28 - 2.00 (m, 3H), 2.00 - 1.64 (m, 7H), 1.60 - 1.55 (m, 3H), 1.53 - 1.18 (m, 11H), 1.14 (s, 3H), 1.08 (d, $J=7.8$ Hz, 1H), 1.03

20 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H)

Step 3: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-formyl-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

25 **cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate**

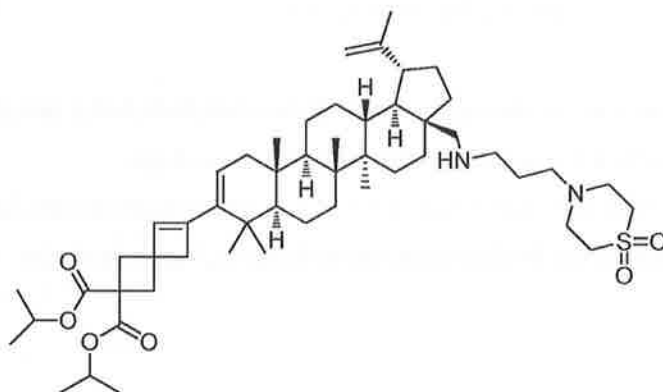


The title compound was prepared following the method for the preparation of Example 1, Step 1 described above, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-formyl-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate as the reactant (83 % yield). MS: m/e 687.5 (M+H)⁺, 4.16 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 9.68 (d, J=1.3 Hz, 1H), 5.86 (s, 1H), 5.51 (dd, J=6.1, 1.9 Hz, 1H), 5.16 - 4.97 (m, 2H), 4.77 (d, J=1.5 Hz, 1H), 4.64 (s, 1H), 2.89 (td, J=11.1, 5.9 Hz, 1H), 2.74 - 2.66 (m, 4H), 2.61 -
- 10 2.49 (m, 2H), 2.21 - 2.01 (m, 3H), 1.96 - 1.18 (m, 33H), 1.17 (s, 3H), 1.05 (m, 4H), 0.98 (s, 3H), 0.94 (s, 3H), 0.81 (s, 3H)

Step 4: Preparation of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-5a,5b,8,8,11a-

- 15 **pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate**



To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-formyl-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (100 mg, 0.146 mmol) from Step 3 in DCE (2 mL) was added acetic acid (0.017 mL, 0.291 mmol) and 4-(3-aminopropyl)thiomorpholine 1,1-dioxide (56.0 mg, 0.291 mmol). The mixture was stirred at RT for 2h, then to the mixture was added sodium triacetoxyborohydride (154 mg, 0.728 mmol) and it was stirred for 24 hours. The mixture was diluted with 7 mL of sat. NaHCO₃ and extracted with dichloromethane (3 x 7 mL). The organic layers were combined and dried with Na₂SO₄. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified over a silica gel column eluted with mixture of ethyl acetate and hexanes. The fractions containing the expected product were combined to give the title compound as a white solid (90 mg, 71.6 % yield). MS: m/e 863.9 (M+H)⁺, 3.03 min (method 2). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.85 (s, 1H), 5.54 - 5.43 (m, 1H), 5.14 - 4.96 (m, 2H), 4.68 (d, J=2.0 Hz, 1H), 4.57 (s, 1H), 3.12 - 2.90 (m, 9H), 2.83 - 2.63 (m, 7H), 2.63 - 2.50 (m, 4H), 2.42 (td, J=11.0, 5.8 Hz, 1H), 2.28 - 2.17 (m, 1H), 2.13 - 2.03 (m, 1H), 1.98 - 1.29 (m, 17H), 1.27 - 1.18 (m, 16H), 1.13 (s, 3H), 1.09 - 1.00 (m, 10H), 0.97 (s, 3H), 0.84 - 0.75 (m, 3H).

20

Step 5: To a solution of diisopropyl 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylate (90 mg, 0.104 mmol) in dioxane (3 mL) and MeOH (2 mL) was added 1N NaOH (2 mL, 2 mmol). The mixture was stirred at 50 °C for 12 h. The crude product was purified by preparative HPLC using method 14. The fractions containing the expected product were combined and concentrated to give 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid as a white solid (2 mg, 2.46%). MS: m/e 779.5 (M+H)⁺, 2.31 min (method 2). ¹H NMR (400MHz, DMSO-d₆) δ 6.02 (s, 1H), 5.48 (d, J=4.5 Hz, 1H), 4.71 (s, 1H), 4.60 (s, 1H), 3.12 (d, J=4.8 Hz,

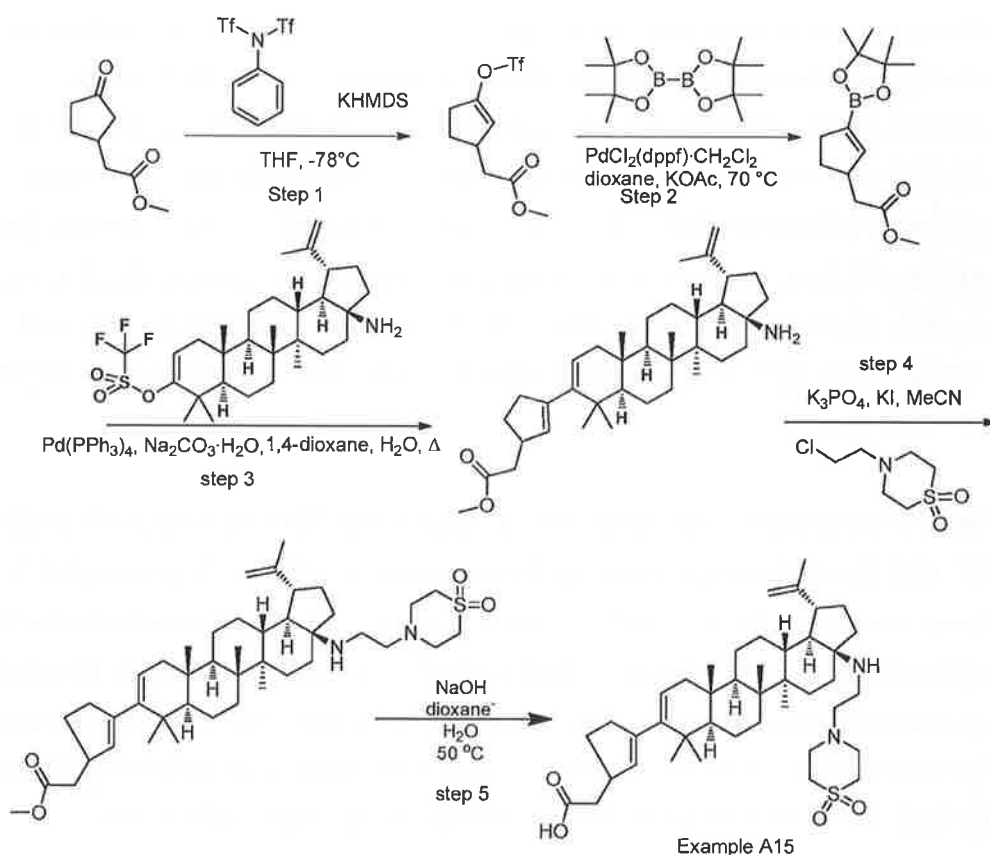
30

5H), 3.01 (br. s., 4H), 2.91 (br. s., 5H), 2.72 - 2.64 (m, 1H), 2.57-2.49 (m 6H), 2.17 - 1.96 (m, 2H), 1.82 (d, $J=5.8$ Hz, 5H), 1.67 (m, 8H), 1.53 - 1.17 (m, 12H), 1.13 (s, 3H), 1.05 (m, 6H), 0.97 (s, 3H), 0.78 (s, 3H).

5 Example A15

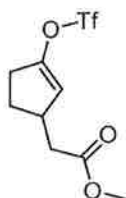
Preparation of 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-en-1-yl)acetic acid

10



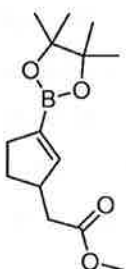
Step 1: Preparation of methyl 2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-en-1-yl) acetate

15



- The title compound was prepared following the procedure described in method 2 for the preparation of intermediate 1, Step 6, using methyl 2-(3-oxocyclopentyl) acetate as the reactant. (50.1% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.66 (q, *J*=2.1 Hz, 1H), 3.73 (br. s., 3H), 3.29 - 3.13 (m, 1H), 2.95 - 2.78 (m, 1H), 2.67 - 2.57 (m, 2H), 2.49 - 2.40 (m, 1H), 2.40-2.28 (m, 1H), 1.77 - 1.63 (m, 1H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -73.53 (s, 3F).

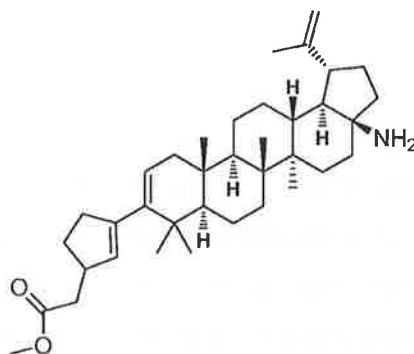
- Step 2: Preparation of methyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-yl) acetate**



- The title compound was prepared following the method for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, Step 2 described above, using methyl 2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-en-1-yl) acetate as the reactant. (65.0 % yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.44 (q, *J*=2.0 Hz, 1H), 3.72 - 3.62 (m, 3H), 3.24 - 3.09 (m, 1H), 2.77 - 2.65 (m, 1H), 2.49 - 2.38 (m, 1H), 2.38 - 2.24 (m, 1H), 2.21 - 2.09 (m, 2H), 1.52 - 1.38 (m, 1H), 1.29 (s, 12H).

Step 3: Preparation of methyl 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)acetate

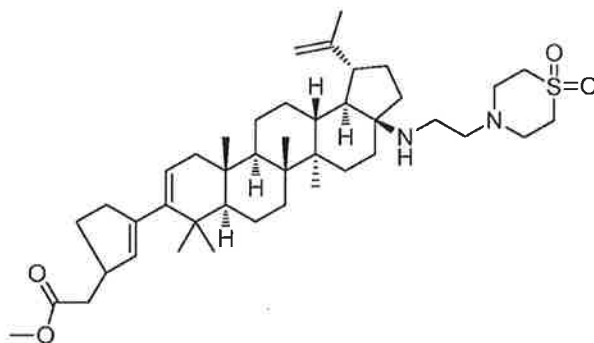


- 5 The title compound was prepared as a mixture of diastereomers in 55.7 % yield following the method for the preparation of Example 1, Step 1 described above, using (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 2-(3-(4,4,5,5-
- 10 tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-yl)acetate as the reactant. MS: m/e 531.5 (M-16)⁺, 2.69 min (method 3). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.54 (s, 1H), 5.50 - 5.44 (m, 1H), 4.73 (s, 1H), 4.60 (s, 1H), 3.67 (s, 3H), 3.14 (t, J=7.0 Hz, 1H), 2.81 - 2.61 (m, 1H), 2.59 - 2.27 (m, 5H), 2.16 - 1.96 (m, 4H), 1.79 - 1.18 (m, 20H), 1.09-1.02 (m, 11H), 0.96 (s, 3H), 0.85 (s, 3H).

15

Step 4: Preparation of methyl 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)acetate

20



The title compound was prepared following the method of Example 1, Step 2 described above, using methyl 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

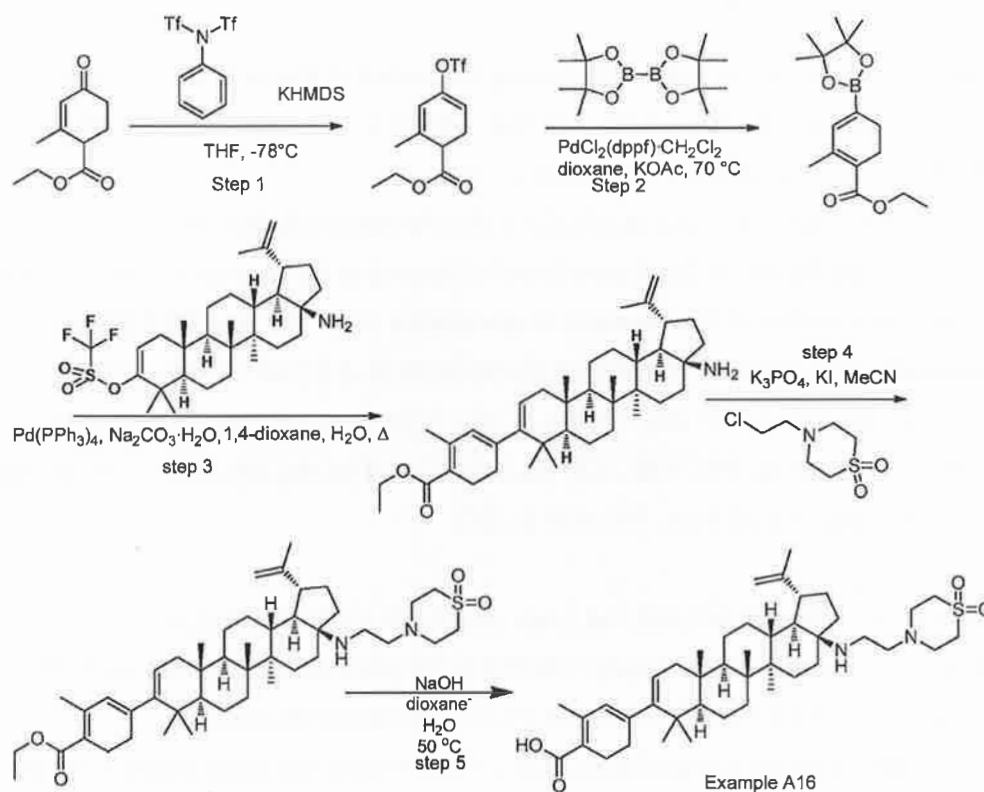
- 5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)acetate as the reactant. The product was isolated as a mixture of diastereomers in quantitative yield. MS: m/e 709.8 (M+H)⁺, 3.126 min (method 3). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.60 - 5.52 (m, 1H), 5.50 - 5.45 (m, 1H), 4.71 (br. s., 1H), 4.59 (br. s., 1H), 3.76 - 3.59 (m, 3H), 3.17 - 2.96 (m, 13H), 2.76 - 2.52 (m, 4H), 2.50 - 2.27 (m, 3H), 2.22 - 1.98 (m, 3H), 1.95 - 1.21 (m, 20H), 1.13 - 1.01 (m, 11H), 0.94 (s, 3H), 0.83 (s, 3H).

Step 5: 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

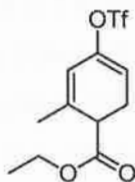
- 15 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)acetic acid was prepared following the method for the preparation of Example 4, Step 3 described above, purified by prep HPLC with method 8, using methyl 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
- 20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)acetate as the reactant. The product was obtained as a mixture of diastereomers in 3 % yield. MS: m/e 695.8 (M+H)⁺, 2.542 min (method 3). ¹H NMR (400MHz, METHANOL-d₄) δ 5.68 - 5.54 (m, 1H), 5.51 - 5.38 (m, 1H), 4.74 (br. s., 1H), 4.64 (s, 1H), 3.22 - 3.00 (m, 9H), 2.98 - 2.69 (m, 5H), 2.65 - 2.31 (m, 2H), 2.31 - 2.18 (m, 2H), 2.06 (m, 2H), 1.97 - 1.83 (m, 9H), 1.77 - 1.68 (m, 3H), 1.66 - 1.22 (m, 12H), 1.17 (s, 3H), 1.09 (m, 2H), 1.02 (m, 6H), 0.87 (s, 3H).
- 25

Example A16

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methylcyclohexa-1,3-dienecarboxylic acid

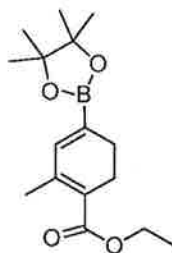


10 **Step 1: Preparation of ethyl 2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohexa-2,4-dienecarboxylate**



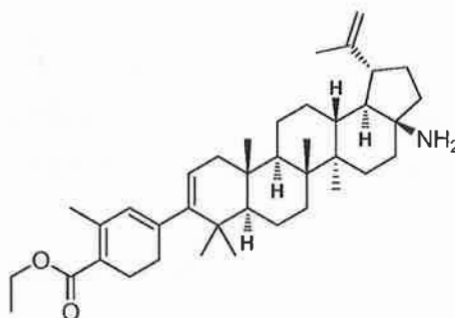
The title compound was prepared following the procedure described in Method 2 for the preparation of Intermediate 1, Step 6, using ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate as the reactant. (62.7 % yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.93 (t, *J*=1.3 Hz, 1H), 4.30 - 4.09 (m, 2H), 2.83 - 2.68 (m, 2H), 2.62 - 2.43 (m, 2H), 2.18 (t, *J*=1.9 Hz, 3H), 1.37 - 1.20 (m, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -73.63 (s, 3F).

Step 2: Preparation of ethyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexa-1,3-dienecarboxylate



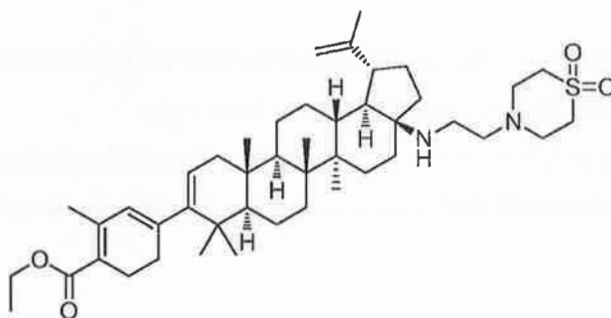
The title compound was prepared following the method for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, Step 2 described above in page 65-67, using ethyl 2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohexa-2,4-dienecarboxylate as the reactant. (57.8 % yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.64 (t, *J*=1.6 Hz, 1H), 4.28 - 4.15 (m, 2H), 2.46 - 2.32 (m, 2H), 2.29 - 2.19 (m, 2H), 2.18 (t, *J*=1.8 Hz, 3H), 1.38 - 1.25 (m, 15H).

Step 3: Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methylcyclohexa-1,3-dienecarboxylate



The title compound was prepared following the method for the preparation of Example 1, Step 1 described above, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and ethyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexa-1,3-dienecarboxylate as reactants. MS: m/e 557.4 (M-16)⁺, 2.47 min (method 2). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.65 (s, 1H), 5.28 (d, J=5.8 Hz, 1H), 4.72 (s, 1H), 4.59 (s, 1H), 4.25 - 4.16 (m, 2H), 2.62 - 2.48 (m, 1H), 2.48 - 2.34 (m, 2H), 2.31 - 2.17 (m, 2H), 2.15 (s, 3H), 2.09 - 1.97 (m, 2H), 1.80 - 1.35 (m, 17H), 1.35 - 1.18 (m, 9H), 1.18 - 1.04 (m, 6H), 1.02 - 1.00 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H).

Step 4: Preparation of ethyl 4-((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methylcyclohexa-1,3-dienecarboxylate

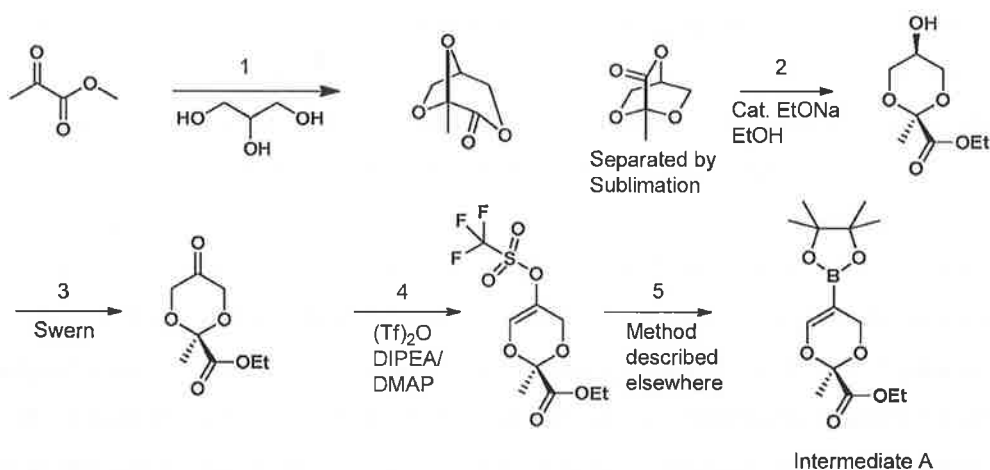


The title compound was prepared following the method described above in Step 2 for the preparation of 6-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxidothiomorpholino)propyl)amino)methyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)spiro[3.3]hept-5-ene-2,2-dicarboxylic acid (example A14), using ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methylcyclohexa-1,3-dienecarboxylate as the reactant. (quantitative yield). MS: m/e 735.8 (M+H)⁺, 3.41 min (method 3). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.65 (s, 1H), 5.28 (dd, J=6.0, 1.5 Hz, 1H), 4.71 (s, 1H), 4.59 (s, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.15 - 2.97 (m, 8H), 2.73 - 2.51 (m, 4H), 2.50 - 2.38 (m, 3H), 2.22 (q, J=8.3 Hz, 2H), 2.15 (s, 3H), 2.06 - 1.18 (m, 25H), 1.11 - 1.04 (m, 6H), 1.00 (s, 3H), 0.98 - 0.95 (m, 6H), 0.88 (s, 3H).

Step 5: 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methylcyclohexa-1,3-dienecarboxylic acid was prepared in 5.46 % yield following the method described above in Step 3 for the preparation of Example 4, using ethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methylcyclohexa-1,3-dienecarboxylate as the reactant. The crude was purified by preparative HPLC with method 14 to afford the title compound in 83% yield. MS: m/e 707.7 (M+H)⁺, 2.573 min (method 3). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.70 (s, 1H), 5.32 (br. s., 1H), 4.78 (br. s., 1H), 4.65 (br. s., 1H), 3.29 - 3.00 (m, 9H), 2.94 - 2.63 (m, 4H), 2.53 - 2.42 (m, 2H), 2.35 - 2.24 (m, 2H), 2.22 (s, 3H), 2.15 - 2.01 (m, 6H), 2.01 - 1.81 (m, 4H), 1.72 (m, 3H), 1.67 - 1.17 (m, 15H), 1.04 - 0.96 (m, 9H), 0.91 (s, 3H).

Intermediate A

Preparation of (R)-ethyl 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-1,3-dioxine-2-carboxylate



Step 1: Preparation of 1-methyl-2,5,7-trioxabicyclo[2.2.2]octan-6-one. The procedure of Gelas and Thiallier [Carbohydrate Research, 30 (1973) 21-34] was used to prepare a mixture of 5-methyl-3,6,8-trioxabicyclo[3.2.1]octan-4-one and 1-methyl-2,5,7-trioxabicyclo[2.2.2]octan-6-one. Further separation of the isomeric mixture was achieved by vacuum sublimation of the gummy mixture material at 35 micron Hg at bath temperature < 56 °C. The more volatile, symmetrical, desired [2.2.2] product condensed as a hard solid (43%), the other unsymmetrical [3.2.1] isomer remained as a thick gummy substance in the pot (45%). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.80 - 4.77 (m, 1H), 4.14 (d, *J*=1.5 Hz, 4H), 1.57 (s, 3H).

Step 2: Preparation of ethyl 5-hydroxy-2-methyl-1,3-dioxane-2-carboxylate. A solution of sodium ethoxide was prepared by dissolving metallic sodium (0.05 g, 2.175 mmol) in absolute ethanol (15 mL). To this, was added 1-methyl-2,5,7-trioxabicyclo[2.2.2]octan-6-one (1.29 g, 8.95 mmol) from Step 1 forming a clear solution. Ring opening was allowed to proceed at RT for 5 hours. The reaction was quenched by the addition of acidic Dowex resin (50W 8X-200, ~equivalent with respect to the amount of sodium used) with stirring. The mixture was filtered and concentrated into a syrup 2.1 gm (82%). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.32 (q, *J*=7.1 Hz, 2H), 3.99 - 3.89 (m, 1H), 3.57 - 3.49 (m, 2H), 1.54 (s, 3H), 1.36 (t, *J*=7.2 Hz, 3H).

Step 3: Preparation of ethyl 2-methyl-5-oxo-1,3-dioxane-2-carboxylate. To a chilled (-78 °C) DCM solvent (10 mL) under nitrogen was added a 2 M stock solution of oxalyl

chloride (6.03 mL, 12.05 mmol), followed by the slow addition of dimethyl sulfoxide (0.927 mL, 13.06 mmol). Once evolution of gases stopped, stirring continued for another 20 minutes forming a snow white suspension. A solution of the crude ethyl 5-hydroxy-2-methyl-1,3-dioxane-2-carboxylate (Step 2, 1.91 g, 10.04 mmol) in 5 mL of DCM was transferred into the cold Swern solution over a period of 2 minutes via a cannula. The reaction was allowed to proceed at -78 °C for 30 minutes, followed by the slow addition of triethylamine (3.36 mL, 24.10 mmol). The resulting pale suspension was stirred at -78 °C for a further 30 minutes, then at 4 °C (ice bath) for 15 minutes. The Rx was quenched with saturated sodium bicarbonate solution (20 mL), followed by extraction with DCM (5 x 25 mL). The organic layers were combined, evaporated to an oily material (1.81 gm, 96%). ¹H NMR (400MHz, CHLOROFORM-d) δ 4.45 - 4.37 (m, 2H), 4.31 (q, J=7.3 Hz, 2H), 4.33 - 4.26 (m, 2H), 1.58 (s, 3H), 1.36 (t, J=7.2 Hz, 3H).

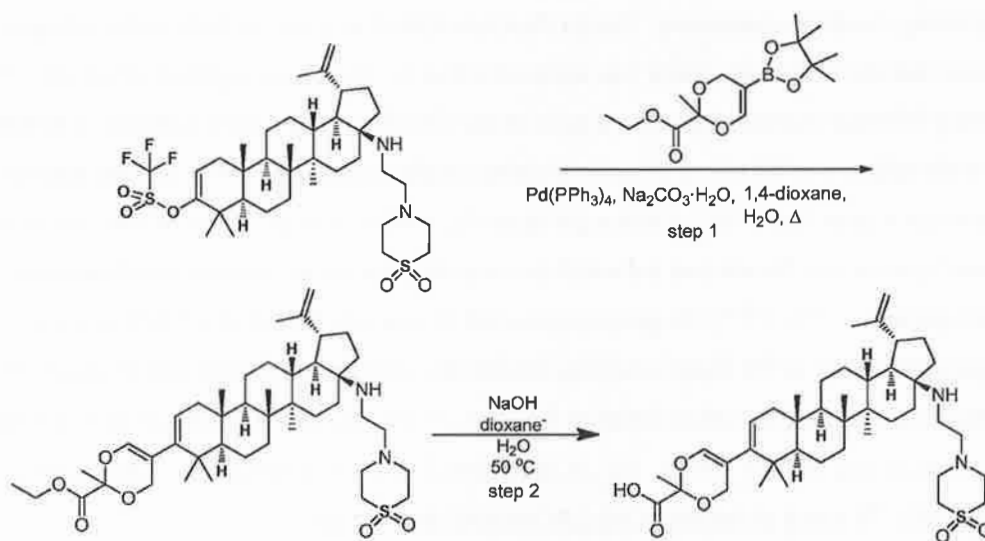
Step 4: Preparation of ethyl 2-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-4H-1,3-dioxine-2-carboxylate. To a chilled (-78 °C) solution of ethyl 2-methyl-5-oxo-1,3-dioxane-2-carboxylate (350 mg, 1.860 mmol) and N,N-dimethylpyridin-4-amine (250 mg, 2.046 mmol) in DCM (4 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.356 mL, 2.046 mmol) and trifluoromethanesulfonic anhydride (0.344 mL, 2.046 mmol) forming a reddish suspension. The mixture was stirred in a dry-ice bath under nitrogen such that the bath temperature was allowed to rise to -15 °C over a period of 4 hours. The crude reaction mixture was diluted with 20 mL DCM forming a clear solution, followed by the addition of 20 mL of hexanes forming a light suspension. It was quickly filtered through a short bed (~½") of silica gel (type-H), washed with a 1:1 v/v mixture of DCM and hexanes, the filtrate was collected for concentration under vacuum at sub-ambient temperature (~15 - 17 °C) to give a semi-solid. It was only briefly dried before it was stored at -20 °C in the fridge readying for the next step without further purification. ¹H NMR (400MHz, CHLOROFORM-d) δ 6.93 (t, J=1.6 Hz, 1H), 4.56 (dd, J=15.1, 1.5 Hz, 1H), 4.35 (dd, J=14.9, 1.9 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 1.68 (s, 3H), 1.34 (t, J=7.2 Hz, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -72.61.

Step 5: To a crude sample (Step 4) of ethyl 2-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-4H-1,3-dioxine-2-carboxylate (68 mg, 0.212 mmol) was added reagents: potassium

acetate (50.0 mg, 0.510 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (64.7 mg, 0.255 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (8.67 mg, 10.62 μ mol), and finally dioxane (2 mL). The reaction vessel was rapidly chilled to -78 °C, purged with nitrogen 4 times. The frozen mixture was allowed to warm into a bright orange solution. It was immersed into an oil bath at 60 °C for 100 minutes. The flask was removed from the oil bath, cooled to RT and filtered through a short bed of silica gel, washed with a 1:1 mixture of DCM and Hexanes. All the volatile solvents were evaporated at RT and the crude product was sufficiently pure for the next step without further purification. ¹H NMR (400MHz, CHLOROFORM-d) δ 7.04 (t, J =1.8 Hz, 1H), 4.45 - 4.39 (m, 1H), 4.30 (dd, J =15.7, 1.9 Hz, 1H), 4.31 - 4.24 (m, 2H), 1.64 (s, 3H), 1.32 (t, J =7.2 Hz, 3H), 1.27 (s, 12H).

Example A17

Preparation of 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methyl-4H-1,3-dioxine-2-carboxylic acid

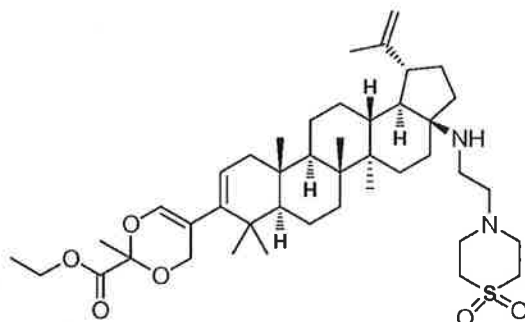


Example A17

20

Step 1: Preparation of ethyl 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-

yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methyl-4H-1,3-dioxine-2-carboxylate



5

The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

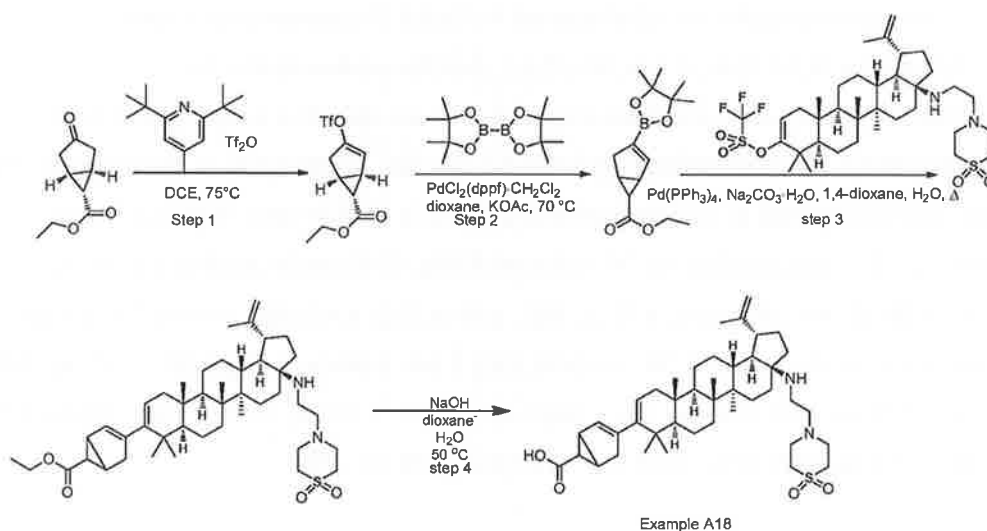
10 cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and ethyl 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-1,3-dioxine-2-carboxylate as the reactants. The product was isolated as a mixture of diastereomers in 13.3 % yield. MS: m/e 741.55 (M+H)⁺, 2.72 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.35 - 6.30 (m, 1H), 5.36 (d, J=5.5 Hz, 1H), 4.73 (s, 1H), 4.60 (s, 1H), 4.42 (ddd, J=15.4, 7.6, 1.4 Hz, 1H), 4.33 - 4.21 (m, 2H), 4.20 - 4.12 (m, 1H), 3.14 - 3.00 (m, 11H), 2.80 - 2.47 (m, 2H), 2.12 - 1.73 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.55 - 1.19 (m, 11H), 1.10 - 1.02 (m, 12H), 1.00 - 0.94 (m, 6H), 0.92 - 0.87 (m, 3H), 0.86 - 0.78 (m, 6H).

Step 2: 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methyl-4H-1,3-dioxine-2-carboxylic acid was prepared following the method described in step 3 for the preparation of Example 4 using ethyl 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-methyl-4H-1,3-dioxine-2-carboxylate as the reactant. The

crude was purified by prep HPLC with method 13 to afford the title compound as a mixture of diastereomers in 17.8% yield. MS: m/e 713.8 ($M+H$)⁺, 2.41 min (method 3). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 6.41 - 6.27 (m, 1H), 5.41 - 5.29 (m, 1H), 4.79 - 4.70 (m, 1H), 4.67 - 4.61 (m, 1H), 4.54 - 4.39 (m, 1H), 4.29 - 4.12 (m, 1H), 3.14 (br. s., 13H), 2.39 - 1.81 (m, 15H), 1.71 (s, 3H), 1.65-1.2 (m, 10H), 1.11 (br. s., 3H), 1.01 (br. s., 6H), 0.90 (br. s., 3H), 0.83 (br. s., 3H).

Example A18

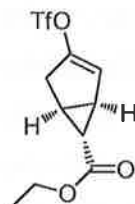
Preparation of 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid



Example A18

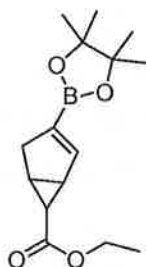
15

Step 1: Preparation of (1S,5S,6R)-ethyl 3-(((trifluoromethyl)sulfonyl)oxy)bicyclo[3.1.0]hex-2-ene-6-carboxylate



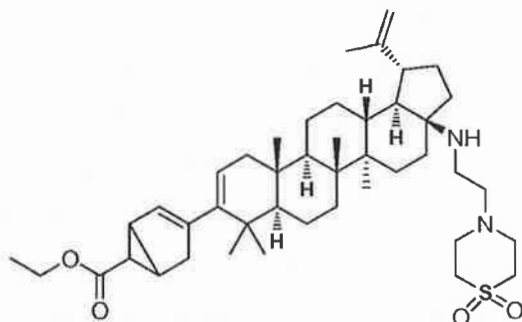
The title compound was prepared in 34.5 % yield following the procedure described in WO 2012/003497, using (±)-(1R,5S,6R)-ethyl 3-oxobicyclo[3.1.0]hexane-6-carboxylate (racemic fragment unless otherwise noted) as the reactant. And (±)-(1R,5S,6R)-ethyl 3-oxobicyclo[3.1.0]hexane-6-carboxylate was prepared following porcedures described in WO 2011/075515. MS: m/e 301.05 (M+H)⁺, 2.689 min (method 8) ¹H NMR (400MHz, CHLOROFORM-d) δ 5.89 (d, J=1.8 Hz, 1H), 4.24 - 4.05 (m, 2H), 3.01 (ddd, J=18.1, 7.2, 1.8 Hz, 1H), 2.70 (d, J=18.3 Hz, 1H), 2.41 (dq, J=7.1, 2.6 Hz, 1H), 2.19 (td, J=7.2, 3.3 Hz, 1H), 1.41 - 1.33 (m, 1H), 1.30 - 1.20 (m, 3H), ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -73.22 (s, 3F).

Step 2: Preparation of ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.1.0]hex-2-ene 6-carboxylate



The title compound was prepared in quantitative yield following the method described in step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, using (±)-(1S,5S,6R)-ethyl 3-(((trifluoromethyl)sulfonyl)oxy)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactant. ¹H NMR (500MHz, CHLOROFORM-d) δ 6.67 (q, J=2.0 Hz, 1H), 4.27 - 3.98 (m, 2H), 2.89 - 2.72 (m, 1H), 2.63 - 2.53 (m, 1H), 2.54 - 2.41 (m, 1H), 2.28 (td, J=6.2, 3.3 Hz, 1H), 1.33 - 1.15 (m, 16H).

Step 3: Preparation of ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate



The title compound was prepared following the method described in step 1 for the
 5 preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.1.0]hex-2-ene 6-carboxylate as the reactants. The title
 10 compound was obtained as a mixture of diastereomers in 54 % yield. MS: m/e 721.55 (M+H)⁺, 2.901 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.81 (dd, J=6.3, 1.5 Hz, 1H), 5.50 - 5.37 (m, 1H), 4.72 (d, J=2.0 Hz, 1H), 4.60 (d, J=0.8 Hz, 1H), 4.19 - 4.05 (m, 3H), 3.11 - 3.00 (m, 7H), 2.97 - 2.82 (m, 1H), 2.74 - 2.43 (m, 6H), 2.17 (td, J=6.6, 3.1 Hz, 1H), 2.09 - 2.01 (m, 2H), 2.00 - 1.73 (m, 3H), 1.70 (s, 3H), 1.66 - 1.18
 15 (m, 20H), 1.16 - 1.01 (m, 11H), 0.97 (m, 3H), 0.83 (m, 3H).

Step 4: 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid was prepared
 20 following the method described in step 3 for the preparation of Example 4 using ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactant. The
 25 crude was purified by prep HPLC with method 13 to afford the title compound as a mixture of diastereomers in 43.1 % yield. MS: m/e 693.55 (M+H)⁺, 2.649 min (method

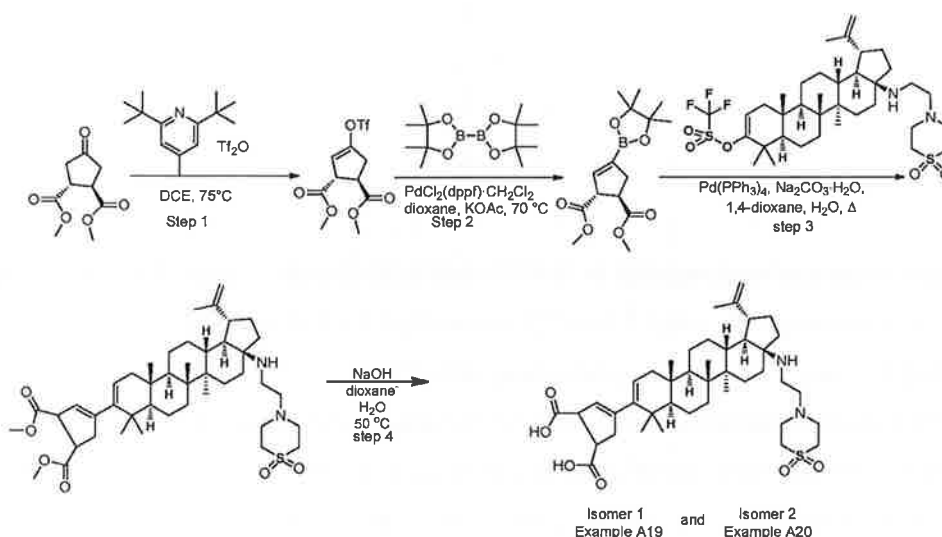
8). ^1H NMR (400MHz, CHLOROFORM- d) δ 5.86 (s, 1H), 5.43 (d, $J=4.5$ Hz, 1H), 4.76 (s, 1H), 4.65 (s, 1H), 3.20 - 3.01 (m, 8H), 3.00 - 2.81 (m, 3H), 2.78 - 2.56 (m, 5H), 2.51 (d, $J=2.3$ Hz, 1H), 2.24 - 1.74 (m, 12H), 1.71 (s, 3H), 1.65 - 1.19 (m, 9H), 1.15 (s, 3H), 1.12 (s, 3H), 1.07 - 1.02 (m, 2H), 1.02 - 0.99 (m, 6H), 0.80 (s, 3H).

5

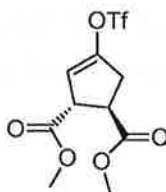
Examples A19 and A20

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-ene-1,2-dicarboxylic acid, Isomer 1 and Isomer 2.

10

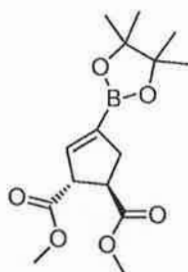


15 Step 1: Preparation of dimethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-ene-1,2-dicarboxylate



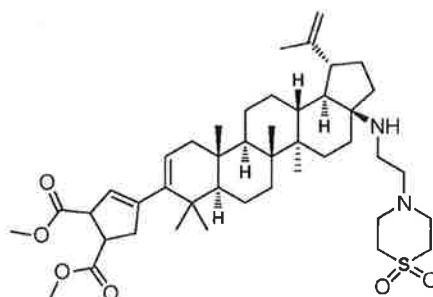
The title compound was prepared in 72.3 % yield following the procedure described in *WO 2012/003497*, using 4-oxo-cyclopentane-trans-1,2-dicarboxylic acid dimethyl ester, as the reactant. MS: m/e 301.05 ($M+H$)⁺, 2.689 min (method 8) ¹H NMR (500MHz, CHLOROFORM-d) δ 5.71 (q, $J=2.1$ Hz, 1H), 4.08 - 3.98 (m, 1H), 3.78 (d, $J=1.7$ Hz, 6H), 3.73 - 3.67 (m, 1H), 3.06 - 2.91 (m, 2H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -73.3 (s, 3F).

Step 2: Preparation of dimethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-ene-trans-1,2-dicarboxylate



The title compound was prepared in 56.8 % yield following the method described in step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, using dimethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-ene-trans-1,2-dicarboxylate as the reactant. ¹H NMR (400MHz, CHLOROFORM-d) δ 6.36 (q, $J=2.3$ Hz, 1H), 4.13 - 4.04 (m, 1H), 3.69 (d, $J=2.5$ Hz, 6H), 3.59 - 3.47 (m, 1H), 3.04 - 2.85 (m, 1H), 2.72 (d, $J=7.3$ Hz, 1H), 1.36 - 1.15 (m, 12H).

Step 3: Preparation of dimethyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-ene-1,2-dicarboxylate



The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-
 5 (1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and dimethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-ene-trans-1,2-dicarboxylate as the reactants. The title compound was obtained as a mixture of diastereomers in 72.7 % yield. MS: m/e
 10 753.6 (M+H)⁺, 2.96 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.55 (s, 1H), 5.53 - 5.49 (m, 1H), 4.71 (d, J=1.8 Hz, 1H), 4.59 (s, 1H), 4.05 - 3.99 (m, 1H), 3.75 - 3.70 (m, 6H), 3.57 - 3.46 (m, 1H), 3.14 - 3.00 (m, 8H), 2.98 - 2.41 (m, 7H), 2.08 (d, J=6.5 Hz, 1H), 2.00 - 1.71 (m, 5H), 1.69 (s, 3H), 1.66 - 1.29 (m, 13H), 1.13 - 1.00 (m, 13H), 0.96 (s, 3H), 0.87 - 0.81 (m, 3H).

15

Step 4: The title compounds were prepared following the method described in step 3 for the preparation of Example 4, using dimethyl 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 20 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-ene-trans-1,2-dicarboxylate as the reactant. The isomers were purified and isolated by prep HPLC with method 13:

Example A19: Isomer 1: (2.2% yield), MS: m/e 725.55 (M+H)⁺, 2.534 min (method 8).

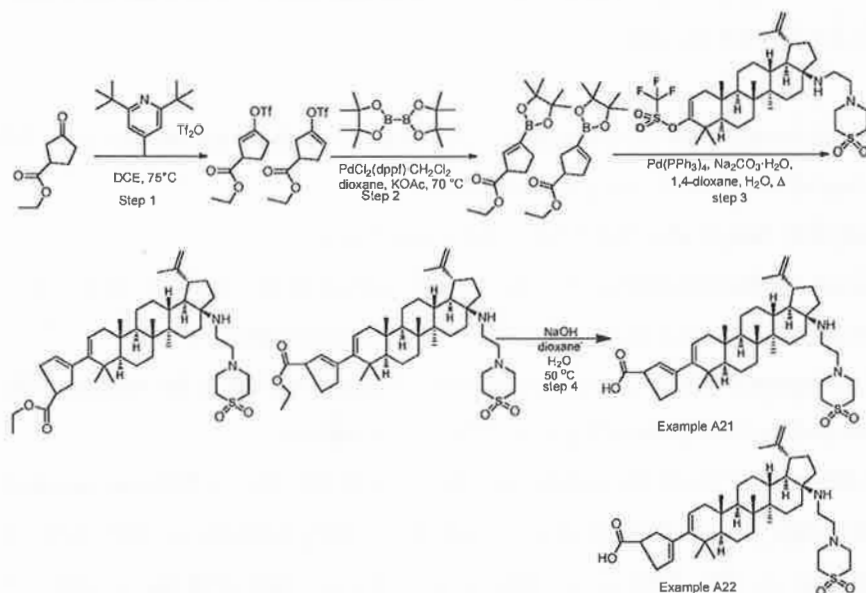
¹H NMR (400MHz, CHLOROFORM-d) δ 5.66 (br. s., 1H), 5.44 (br. s., 1H), 4.76 - 4.70
 25 (m, 1H), 4.68 (br. s., 1H), 3.70 (br. s., 1H), 3.23 - 3.04 (m, 9H), 2.98 (br. s., 2H), 2.91 - 2.76 (m, 4H), 2.66 (br. s., 1H), 2.00 - 1.78 (m, 7H), 1.71 (s, 3H), 1.66 - 1.38 (m, 11H),

1.29 (d, $J=6.8$ Hz, 4H), 1.16 (br. s., 3H), 1.10 (br. s., 3H), 1.02 (br. s., 3H), 0.99 (br. s., 3H), 0.86 (br. s., 3H).

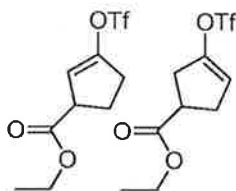
Example A20: Isomer 2: (5% yield), MS: m/e 725.55 ($M+H$)⁺, 2.517 min (method 8). ¹H NMR (400MHz, DICHLOROMETHANE- d_2) δ 5.76 (br. s., 1H), 5.55 (br. s., 1H), 4.75 (br. s., 1H), 4.68 (br. s., 1H), 3.72 - 3.59 (m, 1H), 3.25 - 2.98 (m, 11H), 2.91 (br. s., 4H), 2.62 (br. s., 1H), 2.17 - 1.86 (m, 8H), 1.71 (s, 3H), 1.68 - 1.24 (m, 14H), 1.22 (s, 3H), 1.14 - 1.07 (m, 6H), 1.04 (br. s., 3H), 0.88 (br. s., 3H).

Example A21 and Example A22

- 10 **Preparation of 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-enecarboxylic acid and 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-enecarboxylic acid**



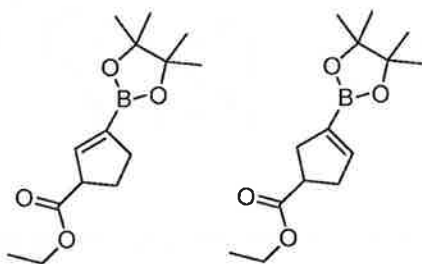
Step 1: Preparation of ethyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-enecarboxylate and ethyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-enecarboxylate



5

The title compounds were prepared following the procedure described in *WO 2012/003497*, using ethyl 3-oxocyclopentanecarboxylate, as the reactant. The product was obtained as a mixture of two isomers in 84% yield. MS: m/e 289.08 ($M+H$)⁺, 2.20 min (method 3). Ethyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-enecarboxylate: ¹H NMR (400MHz, CHLOROFORM-*d*) δ 5.72 (q, $J=2.1$ Hz, 1H), 4.27 - 4.05 (m, 2H), 3.67 - 3.56 (m, 1H), 2.78 - 2.71 (m, 2H), 2.43 - 2.17 (m, 2H), 1.36 - 1.18 (m, 3H). Ethyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-enecarboxylate: ¹H NMR (400MHz, CHLOROFORM-*d*) δ 5.60 (quin, $J=2.3$ Hz, 1H), 4.20 - 4.04 (m, 2H), 3.35 - 3.21 (m, 1H), 3.06 - 2.93 (m, 1H), 2.88 - 2.79 (m, 1H), 2.71 - 2.57 (m, 2H), 1.31 - 1.20 (m, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -73.3 (s, 3F) for both structures.

Step 2: Preparation of ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-enecarboxylate and ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-enecarboxylate

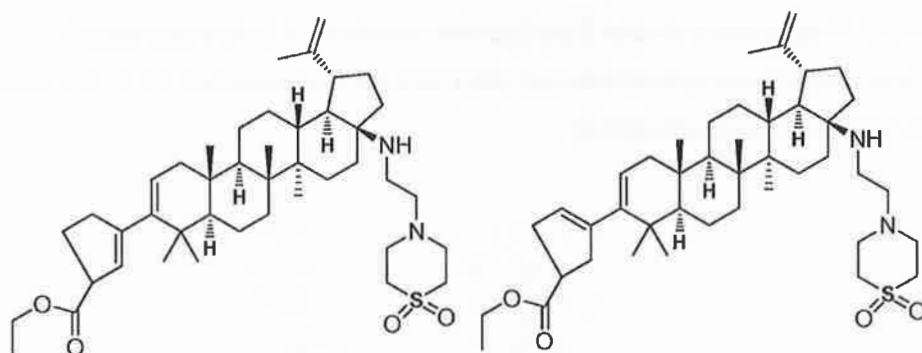


The title compounds were prepared following the method described on step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-

ene-2-carboxylate, using the mixture of ethyl 3-
 (((trifluoromethyl)sulfonyl)oxy)cyclopent-2-enecarboxylate and ethyl 3-
 (((trifluoromethyl)sulfonyl)oxy)cyclopent-3-enecarboxylate as the reactant. The product
 was obtained as a mixture of two isomers in 69.9 % yield. Ethyl 3-(4,4,5,5-tetramethyl-
 5 1,3,2-dioxaborolan-2-yl)cyclopent-2-enecarboxylate: ^1H NMR (400MHz,
 CHLOROFORM-d) δ 6.53 - 6.37 (m, 1H), 4.24 - 4.04 (m, 2H), 3.75 - 3.55 (m, 1H), 2.69
 - 2.56 (m, 1H), 2.52 - 2.40 (m, 1H), 2.28 - 2.06 (m, 2H), 1.33 - 1.19 (m, 15H). Ethyl 3-
 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-enecarboxylate: ^1H NMR
 (400MHz, CHLOROFORM-d) δ 6.53 - 6.34 (m, 1H), 4.24 - 4.04 (m, 2H), 3.13 (tt, $J=9.3$,
 10 7.3 Hz, 1H), 2.91 - 2.68 (m, 4H), 1.32 - 1.24 (m, 15H).

**Step 3: Preparation of ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-
 (1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-
 yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 15 cyclopenta[a]chrysen-9-yl)cyclopent-2-enecarboxylate and ethyl 3-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
 dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)cyclopent-3-enecarboxylate**

20



The title compounds were prepared following the method described in step 1 for the
 preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-
 25 (1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and the mixture of ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-enecarboxylate and ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-enecarboxylate

as the reactants. The product was obtained as a mixture of two isomers in 77 % yield.

- 5 MS: m/e 709.65 (M+H)⁺, 2.961 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.71 - 5.32 (m, 2H), 4.73 (d, $J=2.0$ Hz, 1H), 4.61 (d, $J=1.3$ Hz, 1H), 4.23 - 4.09 (m, 2H), 3.71 - 2.08 (m, 19H), 2.00 - 1.73 (m, 4H), 1.71 (s, 3H), 1.67 - 1.18 (m, 18H), 1.14 - 1.04 (m, 11H), 1.00 - 0.95 (m, 3H), 0.89 - 0.83 (m, 3H).

- 10 **Step 4:** The title compounds were prepared following the method described in step 3 for the preparation of Example 4, using the mixture of ethyl 3-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

- 15 cyclopenta[a]chrysen-9-yl)cyclopent-2-enecarboxylate and ethyl 3-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)cyclopent-3-enecarboxylate as the reactant. The products were

- 20 purified and isolated by preparative HPLC with method 13 to afford two isomeric products:

Example A21: 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

- 25 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)cyclopent-2-enecarboxylic acid: (1.7% yield), MS: m/e 681.55

(M+H)⁺, 2.63 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.71 - 5.44 (m, 2H), 4.73 (s, 1H), 4.62 (s, 1H), 3.67 (br. s., 1H), 3.19 - 3.01 (m, 8H), 2.88 - 2.47 (m, 7H), 2.24 - 2.06 (m, 3H), 1.72 (s, 3H), 1.50 - 1.21 (m, 16H), 1.16 - 1.03 (m, 14H), 0.99 (s, 3H),

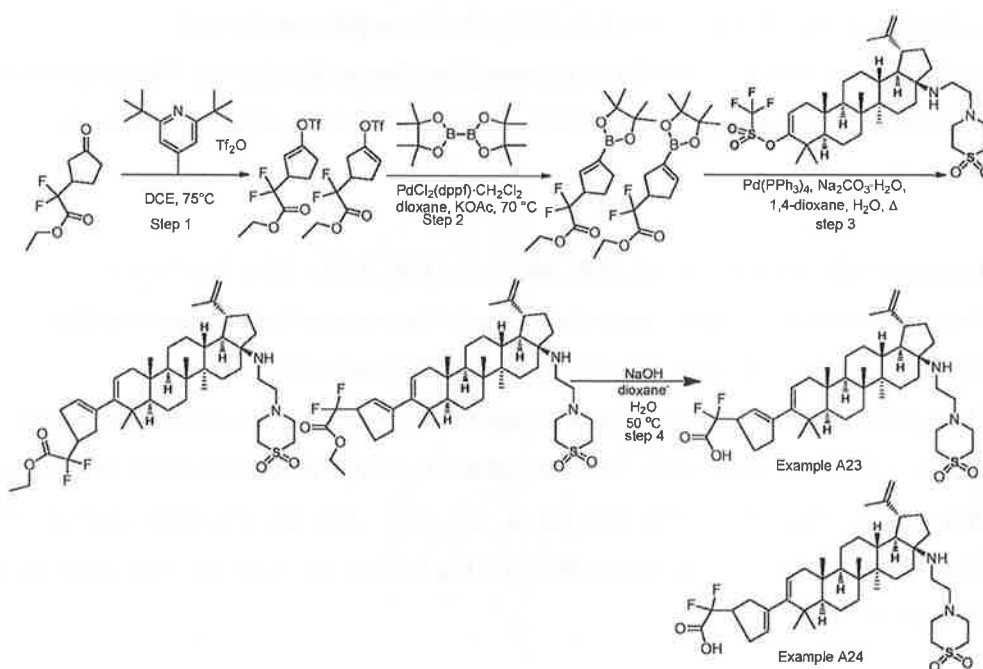
- 30 0.90 (br. s., 3H).

Example A22: 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

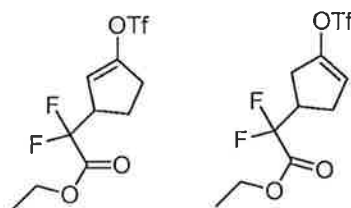
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-enecarboxylic acid: (2.1% yield). MS: m/e 681.55 (M+H)⁺, 2.65 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.68 - 5.44 (m, 2H), 4.78 - 4.69 (m, 1H), 4.65 - 4.57 (m, 1H), 3.09 (m, 8H), 2.95 - 2.42 (m, 8H), 2.30 - 1.77 (m, 3H), 1.71 (s, 3H), 1.67 - 1.20 (m, 17H), 1.17 - 1.02 (m, 13H), 1.00 - 0.97 (m, 3H), 0.87 (s, 3H).

Example A23 and Example A24

Preparation of Preparation of 2-(3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)-2,2-difluoroacetic acid and 2-(3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-3-en-1-yl)-2,2-difluoroacetic acid



Step 1: Preparation of ethyl 2,2-difluoro-2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)acetate and ethyl 2,2-difluoro-2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-en-1-yl)acetate



5

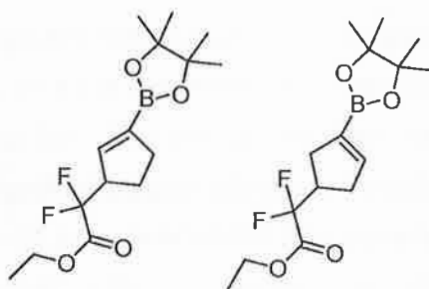
The title compounds were prepared following the procedure described in *WO 2012/003497*, using ethyl 2,2-difluoro-2-(3-oxocyclopentyl)acetate (prepared as described below) as the reactant. The product was obtained as a mixture of isomers in 36.6% yield.

- Isomer 1: Ethyl 2,2-difluoro-2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)acetate: ^1H NMR (400MHz, CHLOROFORM-*d*) δ 5.71 - 5.55 (m, 1H), 4.48 - 4.26 (m, 2H), 3.66 - 3.43 (m, 1H), 2.66 - 2.57 (m, 2H), 2.32 - 2.13 (m, 2H), 1.41 - 1.34 (m, 3H).
- Isomer 2: Ethyl 2,2-difluoro-2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-en-1-yl)acetate: ^1H NMR (400MHz, CHLOROFORM-*d*) δ 5.72 - 5.56 (m, 1H), 4.49 - 4.28 (m, 2H), 3.32 - 3.09 (m, 1H), 2.92 - 2.62 (m, 4H), 1.43 - 1.26 (m, 3H).
- ^{19}F NMR (376MHz, CHLOROFORM-*d*) δ -71.69 - -75.04 (m, 3F), -108.53 - -114.83 (m, 2F) for both structures.

The method of Kumadaki et. al. [Journal of Fluorine Chemistry 125 (2004) 509–515] was adapted to the preparation of ethyl 2,2-difluoro-2-(3-oxocyclopentyl)acetate. To a thick-walled, re-sealable tube was placed cyclopent-2-enone (190 mg, 2.314 mmol) and ethyl 2-bromo-2,2-difluoroacetate (900 mg, 4.43 mmol) in THF (5 mL), followed by ~800 mg of a copper catalyst prepared in accordance with the method of Brewster and Groening in *Org. Synthesis Coll. Vol. II* (1948) 445–446. The suspension was flushed with nitrogen and warmed to 75 °C for 2 hours. After cooling to RT, TMEDA was added (0.4 mL) and the vessel was flushed with nitrogen, re-sealed and warmed to 75 °C for another 16 hours. It was diluted with 5 mL chloroform and 5 mL of hexanes, the suspension was stirred and filtered over a short bed of silica gel (type-H, ~ ½" thick) and washed with mixtures of ethyl acetate and hexanes. The filtrate was concentrated under slight vacuum (25-30

mmHg) at RT to give a pale orange substance. A small amount of the unreacted cyclopent-2-enone was easily removed under this vacuum conditions. The material obtained was used in the next step without further purification (49%). MS: m/e 207.10 ($M+H$)⁺, 3.06 min (method 20). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 4.37 (q, $J=7.3$ Hz, 2H), 3.10 - 2.89 (m, 2H), 2.50 - 2.32 (m, 2H), 2.31 - 2.15 (m, 2H), 2.12 - 1.97 (m, 1H), 1.38 (t, $J=7.2$ Hz, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -110.90 - -111.94 (m, 1F), -113.16 - -114.39 (m, 1F).

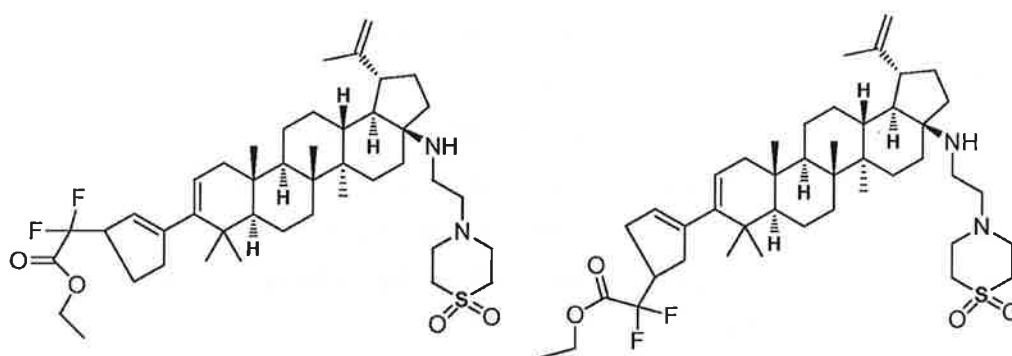
Step 2: Preparation of ethyl 2,2-difluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-yl)acetate and ethyl 2,2-difluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-en-1-yl)acetate



The title compounds were prepared following the method described in step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, using the mixture of ethyl 2,2-difluoro-2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)acetate and ethyl 2,2-difluoro-2-(3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-3-en-1-yl)acetate as the reactant. The product was obtained as a mixture of isomers in 37% yield. Isomer 1: Ethyl 2,2-difluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-yl)acetate: ¹H NMR (400MHz, CHLOROFORM-*d*) δ 6.34 (q, $J=2.2$ Hz, 1H), 4.44 - 4.26 (m, 2H), 3.50 (dddd, $J=14.2, 9.4, 4.9, 2.4$ Hz, 1H), 2.66 - 2.62 (m, 2H), 2.13 - 1.91 (m, 2H), 1.36 (td, $J=7.2, 0.8$ Hz, 3H), 1.28 (d, $J=3.3$ Hz, 12H). Isomer 2: Ethyl 2,2-difluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-en-1-yl)acetate: ¹H NMR (400MHz, CHLOROFORM-*d*) δ 6.41 (s, 1H), 4.42 - 4.25 (m, 2H), 3.15 - 2.92 (m, 1H), 2.67 - 2.41 (m, 4H), 1.40 - 1.33 (m, 3H), 1.31 - 1.26 (m, 12H).

Step 3: Preparation of ethyl 2-(3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-
 en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 5 cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)-2,2-difluoroacetate and ethyl 2-(3-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
 dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)cyclopent-3-en-1-yl)-2,2-difluoroacetate

10



The title compounds were prepared following the method described in step 1 for the
 preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-
 (1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 15 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and the mixture of ethyl 2,2-
 difluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-yl)acetate
 and ethyl 2,2-difluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-3-en-
 1-yl)acetate as the reactants. The product was obtained as a mixture of isomers in 100 %
 20 yield. MS: m/e 759.55 (M+H)⁺, 2.86 min (method 8). ¹H NMR (400MHz,
 CHLOROFORM-d) δ 5.57 - 5.51 (m, 1H), 5.48 (dd, J=4.3, 1.8 Hz, 1H), 4.73 (d, J=1.8
 Hz, 1H), 4.61 (s, 1H), 4.40 - 4.26 (m, 2H), 3.18 - 2.90 (m, 9H), 2.81 - 2.33 (m, 9H), 2.15 -
 1.73 (m, 6H), 1.71 (s, 3H), 1.67 - 1.32 (m, 14H), 1.30 - 1.18 (m, 3H), 1.15 - 1.02 (m,
 11H), 0.98 (s, 3H), 0.86 (s, 3H).

25

Step 4: The title compounds were prepared following the method described in step 3 for the preparation of Example 4, using the mixture of ethyl 2-(3-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

5 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclopent-2-en-1-yl)-2,2-difluoroacetate and ethyl 2-(3-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

10 cyclopenta[a]chrysen-9-yl)cyclopent-3-en-1-yl)-2,2-difluoroacetate

as the reactant. The products were purified and isolated by prep HPLC with method 13 to afford two isomers. Structures were assigned tentatively as follows:

Example A23: Isomer 1: (13% yield). MS: m/e 731.55 (M+H)⁺, 2.72 min (method 8). ¹H

NMR (400MHz, CHLOROFORM-d) δ 5.72 (br. s., 1H), 5.44 (br. s., 1H), 4.74 (s, 1H),

15 4.69 (s, 1H), 3.31 - 2.96 (m, 11H), 2.92 - 2.17 (m, 7H), 2.11 - 1.88 (m, 6H), 1.72 (s, 3H),

1.65 - 1.26 (m, 13H), 1.24 (br. s., 3H), 1.19 (m, 3H), 1.06 (d, J=11.5 Hz, 6H), 0.82 (s, 3H), 0.85 - 0.79 (m, 3H).

Example A24: Isomer 2: (10.4%). MS: m/e 731.55 (M+H)⁺, 2.72 min (method 8). ¹H

NMR (400MHz, CHLOROFORM-d) δ 5.83 (br. s., 1H), 5.43 (d, J=6.3 Hz, 1H), 4.74 (s,

20 1H), 4.70 (s, 1H), 3.26 - 2.54 (m, 18H), 2.24 (d, J=7.3 Hz, 3H), 2.14 - 1.82 (m, 9H), 1.74

(s, 3H), 1.68 - 1.40 (m, 10H), 1.23 (br. s., 6H), 1.07 (d, J=9.5 Hz, 6H), 0.81 (s, 3H).

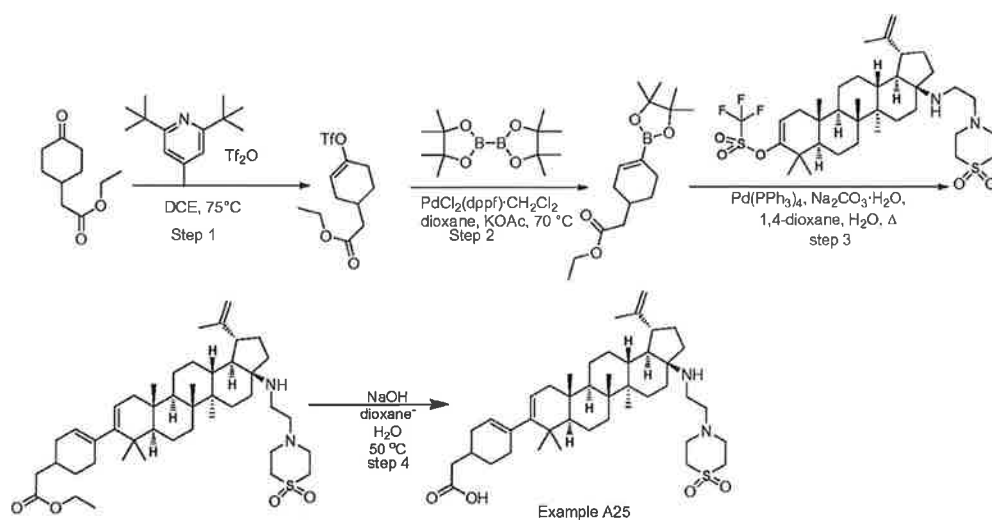
Example A25

Preparation of 2-(4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-

25 **dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-**

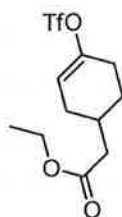
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetic acid



Step 1: Preparation of ethyl 2-(4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)acetate

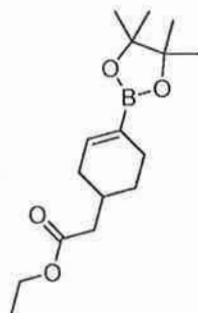
5



The title compound was prepared in 80.0% yield following the procedure described in WO 2012/003497, using ethyl 2-(4-oxocyclohexyl)acetate, as the reactant. ^1H NMR

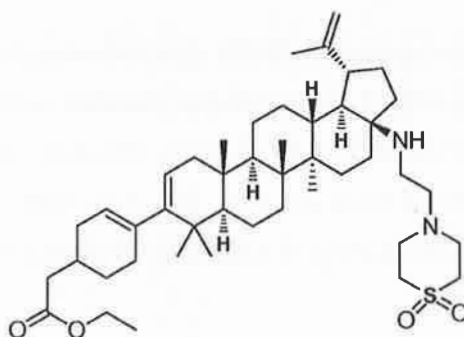
10 (400MHz, CHLOROFORM-d) δ 5.89 - 5.62 (m, 1H), 4.24 - 4.07 (m, 2H), 2.53 - 2.41 (m, 1H), 2.40 - 2.34 (m, 2H), 2.32 (d, $J=7.0$ Hz, 2H), 2.22 - 2.09 (m, 1H), 2.01 - 1.89 (m, 2H), 1.58 - 1.49 (m, 1H), 1.28 (td, $J=7.1, 2.6$ Hz, 3H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -73.897 (s, 3F).

15 **Step 2: Preparation of ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)acetate**



The title compound was prepared following the method described in step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, using ethyl 2-(4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-en-1-yl)acetate as the reactant. (99% yield), MS: m/e 295.2 ($M+H$)⁺, 2.28 min (method 3). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 6.54 (d, $J=2.3$ Hz, 1H), 4.15 (q, $J=7.3$ Hz, 2H), 2.41 - 1.99 (m, 7H), 1.93 - 1.71 (m, 2H), 1.38 - 1.22 (m, 15H).

Step 3: Preparation of ethyl 2-(4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetate



15

The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and ethyl 2-(4-(4,4,5,5-tetramethyl-

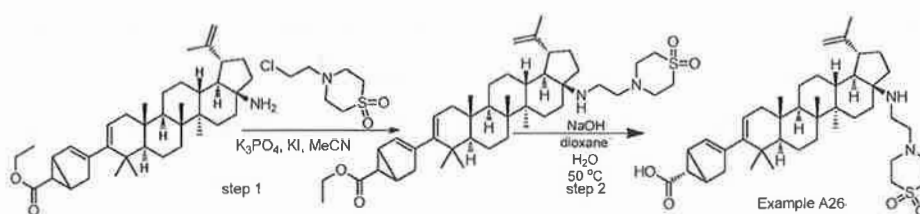
20

1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)acetate as the reactants. The product was obtained as a mixture of diastereomers in 42.7 % yield. MS: m/e 737.65 (M+H)⁺, 2.939 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.32 (br. s., 1H), 5.19 (d, J=5.8 Hz, 1H), 4.72 (d, J=1.8 Hz, 1H), 4.61 (d, J=1.5 Hz, 1H), 4.21 - 4.09 (m, 2H), 3.15 - 2.96 (m, 8H), 2.77 - 2.54 (m, 4H), 2.52 - 2.40 (m, 1H), 2.34 - 2.08 (m, 4H), 2.03 - 1.72 (m, 7H), 1.70 (s, 3H), 1.61 - 1.39 (m, 9H), 1.39 - 1.19 (m, 10H), 1.12 - 1.04 (m, 7H), 1.01 - 0.97 (m, 6H), 0.96 - 0.91 (m, 3H), 0.87 (s, 3H).

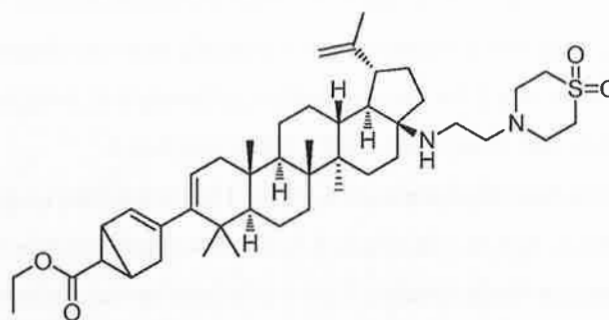
Step 4: 2-(4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetic acid was prepared following the method described in step 3 for the preparation of Example 4, using ethyl 2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetate as the reactant. The crude was purified by prep HPLC with method 15 to afford the title compound as a mixture of diastereomers in 19.9% yield. MS: m/e 709.6 (M+H)⁺, 2.679 min (method 8). ¹H NMR (400MHz, METHANOL-d₄) δ 5.34 (br. s., 1H), 5.22 (d, J=6.3 Hz, 1H), 4.87 (s, 1H), 4.76 (s, 1H), 3.30 - 3.17 (m, 8H), 3.16 - 3.07 (m, 3H), 3.02 - 2.90 (m, 1H), 2.80 (td, J=11.0, 5.4 Hz, 1H), 2.28 (d, J=7.0 Hz, 2H), 2.25 - 2.00 (m, 9H), 1.90 - 1.80 (m, 4H), 1.78 (s, 3H), 1.75 - 1.23 (m, 15H), 1.20 (s, 3H), 1.17 (d, J=2.8 Hz, 1H), 1.13 (s, 3H), 1.03 (s, 1.5H), 1.01 (s, 1.5H), 1.00 (s, 1.5H), 0.97 (s, 1.5H), 0.95 (s, 3H).

Example A26

Preparation of (6S)-3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid



- Step 1: Preparation of 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid**



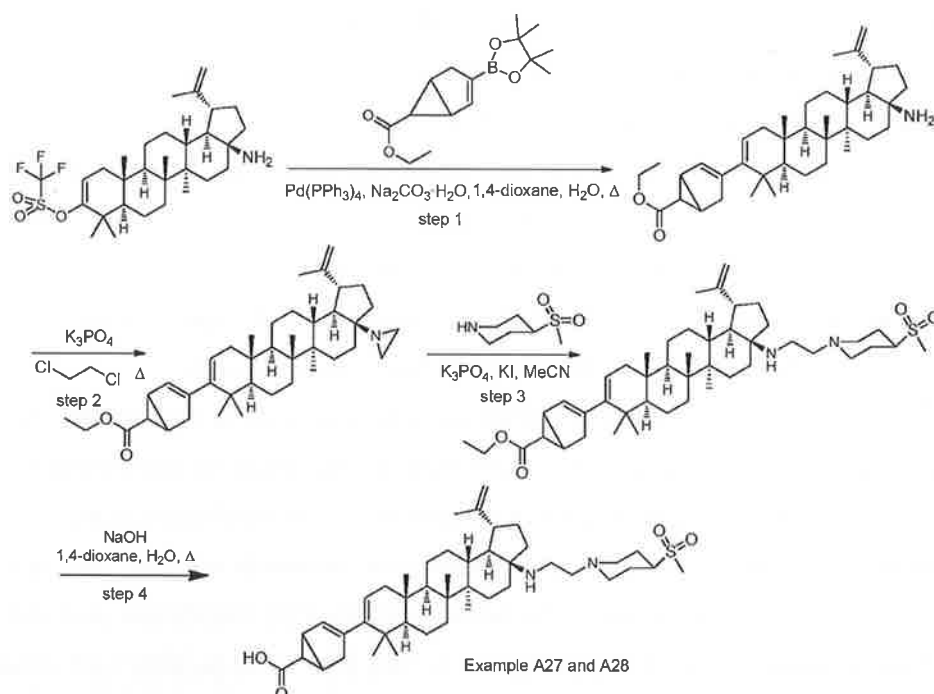
- The title compound was prepared following the method described in step 2 for the preparation of Example 1, using ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactant. The product was obtained in 29.9 % yield as a single isomer. MS: m/e 721.55 ($M+H$)⁺, 2.879 min (method 8). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 5.86 - 5.69 (m, 1H), 5.48 - 5.32 (m, 1H), 4.71 (d, $J=1.8$ Hz, 1H), 4.60 (d, $J=1.5$ Hz, 1H), 4.23 - 3.99 (m, 2H), 3.16 - 2.97 (m, 9H), 2.96 - 2.80 (m, 1H), 2.75 - 2.39 (m, 7H), 2.16 (td, $J=6.6, 3.1$ Hz, 1H), 2.09 - 1.99 (m, 2H), 1.98 - 1.72 (m, 5H), 1.69 (s, 3H), 1.65 - 1.30 (m, 11H), 1.29 - 1.21 (m, 5H), 1.11 (dd, $J=5.3, 2.5$ Hz, 2H), 1.07 (s, 1.5H), 1.06 (s, 3H), 1.03 (d, $J=1.3$ Hz, 3H), 0.97 (s, 1.5H), 0.97 (s, 3H), 0.83 (s, 1.5H), 0.82 (s, 1.5H).

Step 2: 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid compound was prepared following the method described in step 3 for the preparation of Example 4, using ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactant. The crude was purified by preparative HPLC with method 15 to afford the title compound as a single isomer (this isomer can be found in the mixture of isomers obtained in the preparation of example A18). The stereochemistry was arbitrarily assigned. MS: m/e 693.55 (M+H)⁺, 2.65 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.94 (s, 1H), 5.48 (d, J=4.8 Hz, 1H), 4.82 (s, 1H), 4.73 (s, 1H), 3.27 - 3.00 (m, 9H), 2.97 - 2.84 (m, 3H), 2.80 - 2.58 (m, 3H), 2.28 - 2.13 (m, 2H), 2.10 - 1.87 (m, 6H), 1.82 - 1.74 (m, 1H), 1.71 (s, 3H), 1.68 - 1.25 (m, 13H), 1.22 (s, 3H), 1.16 (s, 3H), 1.11-1.07 (m, 2H), 1.06 (s, 6H), 0.99 (d, J=2.3 Hz, 1H), 0.76 (s, 3H).

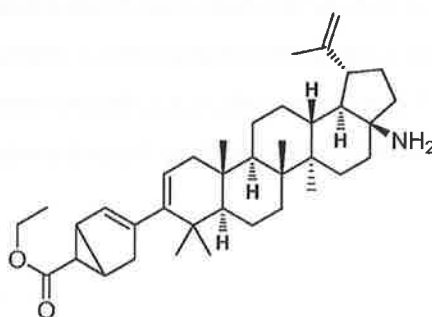
Example A27 and Example A28

20 Preparation of 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (Isomer 1 and Isomer 2)

25



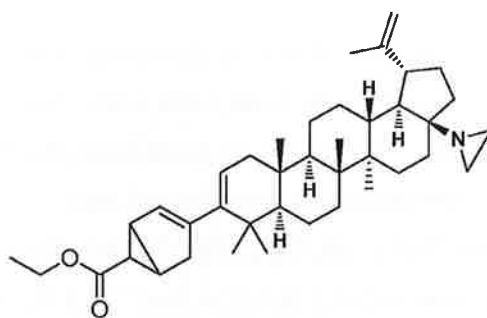
- Step 1: Preparation of ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate**



- The titled compound was prepared in 86.6 % yield following the method described in step 1 for the preparation of Example 1 described above, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and ethyl 3-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactants. MS: m/e 543.5 (M-16)⁺, 2.87 min. ¹H NMR (400MHz, CHLOROFORM-d) δ 5.84 - 5.72 (m, 1H), 5.47 - 5.32 (m, 1H), 4.72 (s, 1H), 4.59 (s, 1H), 4.24 - 3.99 (m, 2H), 3.09 - 2.74 (m, 1H), 2.67 - 2.40 (m, 3H), 2.26 - 2.10 (m, 1H), 2.09 - 1.92 (m, 3H), 1.69 (s, 3H), 1.67 - 1.65 (m, 1H), 1.64 - 1.31 (m, 9H), 1.29 - 1.22 (m, 5H), 1.17 - 1.05 (m, 4H), 1.02 (s, 6H), 0.98 - 0.93 (m, 7H), 0.82 (m, 3H).

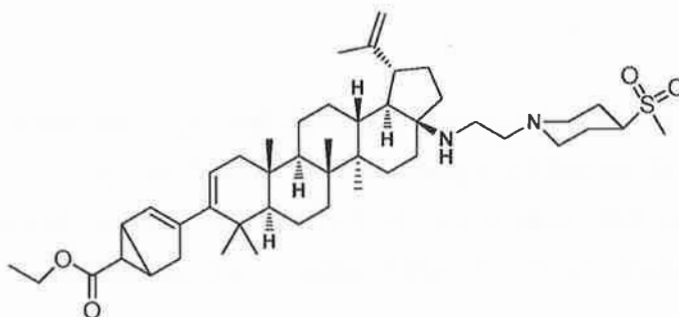
Step 2: Preparation of ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate



To a flame dried 75 mL thick-walled resealable vessel was placed ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (0.453 g, 0.809 mmol) and flame dried potassium phosphate (0.859 g, 4.05 mmol), followed by 1,2-dichloroethane (24 mL) and acetonitrile (12 mL). The reaction mixture was flushed with nitrogen, sealed, and warmed to 130 °C for 36 hours. The crude reaction mixture was cooled to room temperature and filtered through a short bed of silica gel, washed with ethyl acetate to obtain a very pale orange solution, it was evaporated to dryness. White solid was obtained (0.3g, 0.512 mmole, 63.3%), and used as it is. MS: m/e 586.55 (M+H)⁺, 2.791 min.

Step 3: Preparation of ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate

5



The title compound was prepared following the method describe on step 1 for the preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)octadecahydro-1H-cyclopenta[a]chrysen-9(5bH)-one using 4-(methylsulfonyl)piperidine and ethyl 3-

9(5bH)-one using 4-(methylsulfonyl)piperidine and ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactants. The product was obtained as a mixture of diastereomers in 33.2 % yield.

MS: m/e 749.6 (M+H)⁺, 2.794 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.84 - 5.75 (m, 1H), 5.49 - 5.38 (m, 1H), 4.69 (br. s., 1H), 4.59 (br. s., 1H), 4.19 - 4.04 (m, 2H), 3.12 (dd, J=15.6, 12.8 Hz, 1H), 2.98 - 2.74 (m, 7H), 2.68 - 2.51 (m, 5H), 2.45 (d, J=7.5 Hz, 4H), 2.22 - 2.10 (m, 3H), 2.09 - 1.74 (m, 8H), 1.69 (s, 3H), 1.65 - 1.30 (m, 12H), 1.26 (m, 6H), 1.06 (br. s., 5.5H), 1.02 (s, 3H), 0.98 - 0.92 (m, 4.5H), 0.85 - 0.78 (m, 3H).

Step 4: 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid, (Isomer 1 and Isomer 2) were prepared following the method described in step 3 for the preparation of

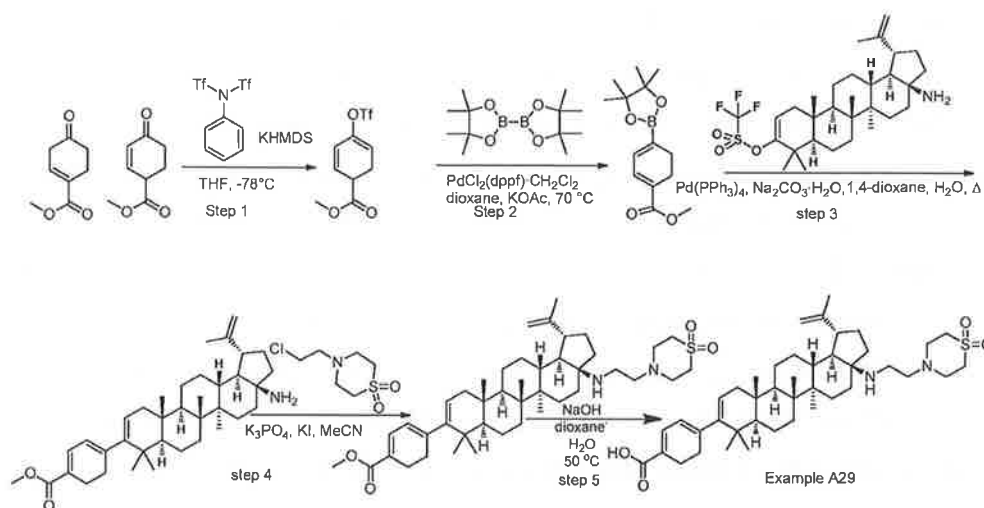
Example 4, using ethyl 3-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate as the reactant. The
5 crude was purified by prep HPLC with method 15, to afford two isomers:

Example A27: Isomer 1: (16.3%), MS: m/e 721.6 (M+H)⁺, 2.613 min (method 8). ¹H NMR (400MHz, METHANOL-d₄) δ 5.82 (d, J=1.5 Hz, 1H), 5.53 - 5.37 (m, 1H), 4.85 (br. s., 1H), 4.74 (br. s., 1H), 3.26 - 3.16 (m, 4H), 3.04 (t, J=9.3 Hz, 1H), 2.97 (s, 3H), 2.95 - 2.82 (m, 2H), 2.82 - 2.71 (m, 2H), 2.67 - 2.52 (m, 2H), 2.48 - 2.35 (m, 2H), 2.26 -
10 1.98 (m, 9H), 1.98 - 1.74 (m, 5H), 1.76 (s, 3H), 1.71 - 1.30 (m, 12H), 1.20 (s, 3H), 1.18 - 1.13 (m, 1H), 1.09 (s, 3H), 1.06 (s, 6H), 1.02 (br. s., 1H), 0.89 (s, 3H).

Example A28: Isomer 2: (13.4%), MS: m/e 721.6 (M+H)⁺, 2.649 min (method 8). ¹H NMR (400MHz, METHANOL-d₄) δ 5.83 (d, J=1.8 Hz, 1H), 5.47 (dd, J=6.4, 1.9 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.29 - 3.17 (m, 4H), 3.04 (d, J=9.0 Hz, 1H), 2.98 (s, 3H),
15 2.94 - 2.71 (m, 4H), 2.68 - 2.57 (m, 2H), 2.44 (dq, J=6.6, 2.2 Hz, 2H), 2.27 - 1.97 (m, 9H), 1.94 - 1.79 (m, 4H), 1.78 (s, 3H), 1.74 - 1.26 (m, 14H), 1.22 (s, 3H), 1.11 (s, 6H), 1.04 - 1.00 (m, 4H), 0.89 (s, 3H).

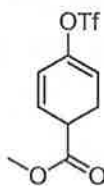
Example A29

20 **Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylic acid**



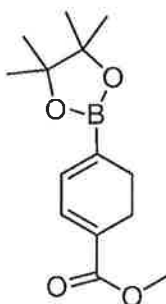
Step 1: Preparation of methyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohexa-1,3-dienecarboxylate

5



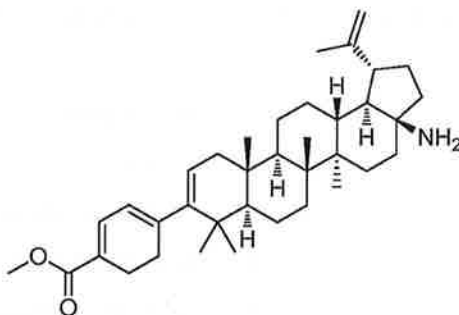
The title compound was prepared in 53.9 % yield following the procedure described in step 6 of method 2 for the preparation of intermediate 1, using methyl 4-oxocyclohex-1-enecarboxylate and methyl 4-oxocyclohex-2-enecarboxylate as the reactants. Methyl 4-oxocyclohex-1-enecarboxylate and methyl 4-oxocyclohex-2-enecarboxylate were prepared following the procedures described in *Tet. Lett. Vol. 53, issue 7, page 819-821*. m/e 287.05 ($M+H$)⁺, 2.435 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.96 (dt, $J=6.3$, 1.5 Hz, 1H), 6.07 (dt, $J=6.4$, 1.4 Hz, 1H), 3.78 (s, 3H), 2.81 - 2.73 (m, 2H), 2.67 - 2.59 (m, 2H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -73.55 (s, 3F).

Step 2: Preparation of methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexa-1,3-dienecarboxylate



The title compound was prepared following the method described in step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, using methyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohexa-1,3-dienecarboxylate as the reactant. (46.6 % yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 7.00 (dt, *J*=5.3, 1.5 Hz, 1H), 6.75 (dt, *J*=5.3, 1.6 Hz, 1H), 3.74 (s, 3H), 2.42 - 2.35 (m, 2H), 2.34 - 2.27 (m, 2H), 1.26 (s, 12H).

Step 3: Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate



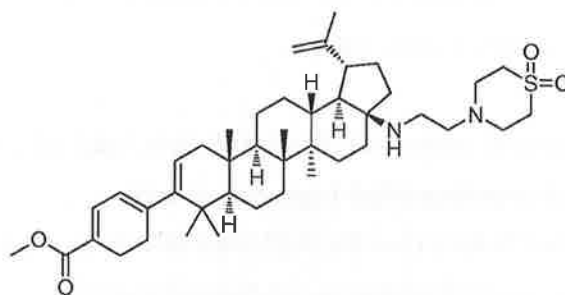
15

The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 4-(4,4,5,5-tetramethyl-

20

1,3,2-dioxaborolan-2-yl)cyclohexa-1,3-dienecarboxylate as the reactants. (60.8 % yield).
 MS: m/e 529.5 (M-16)⁺, 2.816 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d)
 δ 6.99 (d, $J=5.8$ Hz, 1H), 5.78 (d, $J=5.8$ Hz, 1H), 5.27 (dd, $J=6.0, 1.8$ Hz, 1H), 4.70 (d,
 $J=2.0$ Hz, 1H), 4.57 (d, $J=1.3$ Hz, 1H), 3.72 (s, 3H), 2.52 (td, $J=10.8, 5.3$ Hz, 1H), 2.48 -
 5 2.39 (m, 1H), 2.36 - 2.29 (m, 1H), 2.09 - 1.95 (m, 2H), 1.76 - 1.20 (m, 22H), 1.66 (s, 3H),
 1.05 (s, 3H), 0.98 (s, 3H), 0.94 (s, 6H), 0.86 (s, 3H).

**Step 4: Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-
 ((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-
 10 en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate**



15 The title compound was prepared following the method described in step 2 for the
 preparation of Example 1, using methyl 4-
 ((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-
 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate as the reactant. (30.9 % yield).
 20 MS: m/e 707.7 (M+H)⁺, 3.20 min (method 2). ¹H NMR (400MHz, CHLOROFORM-d) δ
 7.00 (d, $J=5.8$ Hz, 1H), 5.78 (d, $J=5.8$ Hz, 1H), 5.30 - 5.23 (m, 1H), 4.68 (d, $J=2.0$ Hz,
 1H), 4.57 (d, $J=1.3$ Hz, 1H), 3.73 (s, 3H), 3.11 - 2.95 (m, 9H), 2.67 - 2.50 (m, 4H), 2.47 -
 2.39 (m, 3H), 2.34 - 2.27 (m, 1H), 2.14 - 1.01 (m, 22H), 1.66 (s, 3H), 1.23 (s, 3H), 1.04
 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.86 (s, 3H).

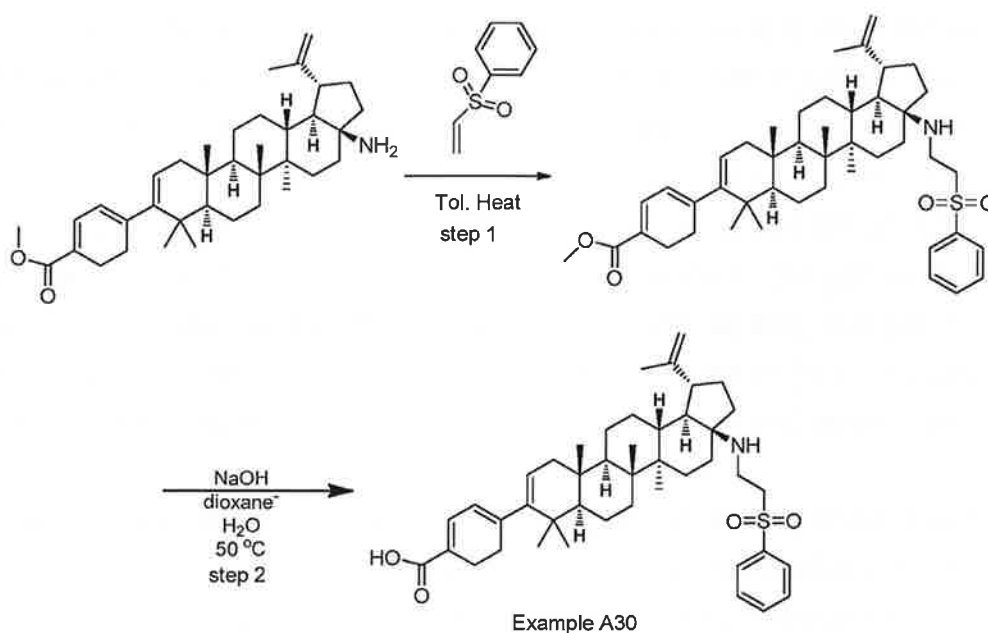
25

**Step 5: 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-
 dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-**

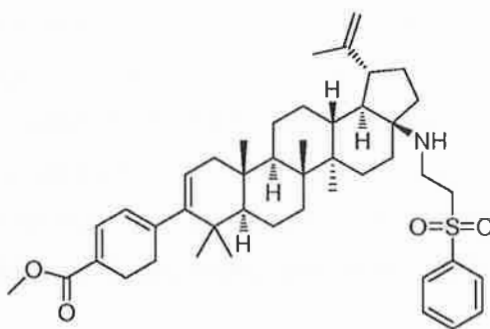
- 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylic acid was following the method described in step 3 for the preparation of Example 4, using methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate as the reactant. The crude was purified by prep HPLC with method 13 to afford the title compound in 34% yield MS: m/e 693.51 (M+H)⁺, 2.2 min (method 2). ¹H NMR (400MHz, CHLOROFORM-d) δ 7.08 (d, J=5.5 Hz, 1H), 5.81 (d, J=5.5 Hz, 1H), 5.29 (d, J=4.8 Hz, 1H), 4.73 (s, 1H), 4.63 (s, 1H), 3.19 - 2.89 (m, 10H), 2.83 - 2.66 (m, 3H), 2.49 - 2.27 (m, 4H), 2.16 - 1.02 (m, 22H), 1.69 (s, 3H), 1.13 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H).

Example A30

- 15 Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(phenylsulfonyl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylic acid



Step 1: Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(phenylsulfonyl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate



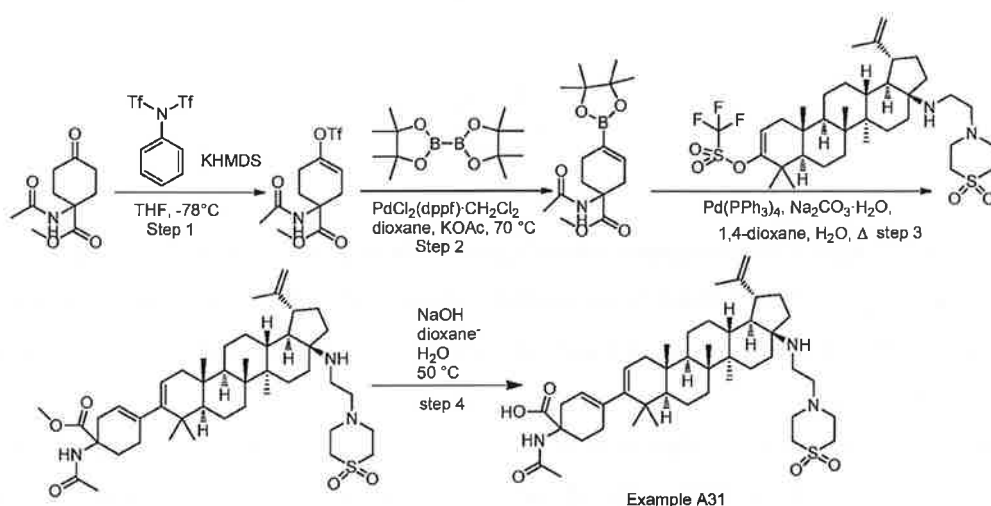
Methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate (200 mg, 0.366 mmol) and (vinylsulfonyl)benzene (80 mg, 0.476 mmol) were dissolved in toluene (1 mL). The solution was warmed to 90 °C for 9 hours. The crude reaction mixture was applied onto a 12 gm silica gel column, purified with 0-10% ethyl acetate/hexanes as eluent to afford the title compound as a white solid (100 mg, 0.14 mmole, 38.2%). MS: m/e 714.53 (M+H)⁺, 2.46 min (method 2). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.03 - 7.89 (m, 2H), 7.73 - 7.66 (m, 1H), 7.66 - 7.57 (m, 2H), 7.08 - 7.01 (m, 1H), 5.83 (d, J=5.5 Hz, 1H), 5.30 (d, J=1.8 Hz, 1H), 4.70 (d, J=2.5 Hz, 1H), 4.65 - 4.55 (m, 1H), 3.82 - 3.71 (m, 3H), 3.42 - 3.24 (m, 2H), 3.03 - 2.86 (m, 1H), 2.86 - 2.70 (m, 1H), 2.56 - 2.40 (m, 3H), 2.40 - 2.26 (m, 1H), 2.09 - 2.00 (m, 1H), 1.98 - 1.85 (m, 1H), 1.85 - 1.73 (m, 2H), 1.71 - 1.67 (m, 3H), 1.67 - 1.38 (m, 7H), 1.37 - 1.11 (m, 12H), 1.10 - 1.07 (m, 3H), 1.04 - 1.01 (m, 3H), 0.98 (d, J=3.3 Hz, 3H), 0.97 - 0.94 (m, 3H), 0.92 - 0.89 (m, 3H).

Step 2: 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(phenylsulfonyl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylic acid was prepared following

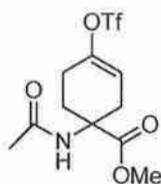
- the method described in step 3 for the preparation of Example 4, using methyl 4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(phenylsulfonyl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohexa-1,3-dienecarboxylate as the reactant. The crude was purified by prep HPLC with method 13 to afford the title compound in 11.3 % yield. MS: m/e 700.55 (M+H)⁺, 2.838 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.05 - 7.92 (m, 2H), 7.78 - 7.67 (m, 1H), 7.65 - 7.53 (m, 2H), 7.17 (d, J=5.8 Hz, 1H), 5.86 (d, J=5.8 Hz, 1H), 5.47 - 5.21 (m, 1H), 4.71 (d, J=2.0 Hz, 1H), 4.60 (s, 1H), 3.33 (td, J=6.1, 2.0 Hz, 2H), 2.92 (dt, J=12.7, 6.2 Hz, 1H), 2.85 - 2.68 (m, 1H), 2.53 - 2.29 (m, 6H), 2.24 - 1.85 (m, 5H), 1.84 - 1.70 (m, 3H), 1.69 (s, 3H), 1.67 - 1.11 (m, 13H), 1.09 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H).

Example A31

- 15 **Preparation of 1-acetamido-4-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid**

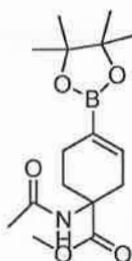


Step 1: Preparation of methyl 1-acetamido-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate



The title compound was prepared following the procedure described on step 6 of method 2 for the preparation of intermediate 1, using methyl 1-acetamido-4-oxocyclohexanecarboxylate, as the reactant. 1-acetamido-4-oxocyclohexanecarboxylate was prepared following the procedures described in *Journal of Chem. Soc., Perkin Trans. I*, 1999, pp. 3375-3379. (84.0 % yield), MS: m/e 346.1 (M+H)⁺, 2.213 min (method ?). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.24 (s, 1H), 5.69 (td, J=3.3, 1.4 Hz, 1H), 3.82 - 3.58 (m, 3H), 2.87 - 2.67 (m, 1H), 2.61 - 2.44 (m, 2H), 2.42 - 2.33 (m, 2H), 2.19 - 2.07 (m, 1H), 2.01 - 1.94 (m, 3H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -74.02 (s, 3F).

Step 2: Preparation of methyl 1-acetamido-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate



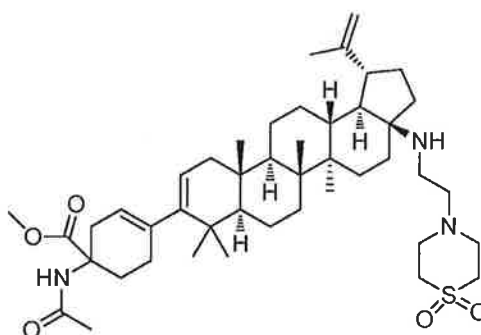
15

The title compound was prepared following the method described in step 2 for the preparation of methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.3]hept-5-ene-2-carboxylate, using methyl 1-acetamido-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate as the reactant. (48.4 % yield). MS: m/e 325.25 (M+H)⁺, 2.126 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.42 (br. s., 1H), 5.90 (s, 1H), 3.83 - 3.59 (m, 3H), 2.65 (d, J=18.8 Hz, 1H), 2.35 (d, J=18.1 Hz, 1H), 2.25 (d, J=11.0 Hz, 2H), 2.13 - 2.03 (m, 1H), 1.98 - 1.90 (m, 3H), 1.88 - 1.75 (m, 1H), 1.36 - 1.18 (m, 12H).

25

Step 3: Preparation of methyl 1-acetamido-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate



The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 1-acetamido-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as the reactants. The product was obtained as a mixture of diastereomers in 65.7 % yield. MS: m/e 766.8 (M+H)⁺, 2.72 min (method 3). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.82 (d, J=3.0 Hz, 1H), 5.26 (br. s., 1H), 5.21 - 5.12 (m, 1H), 4.70 (d, J=2.0 Hz, 1H), 4.58 (d, J=1.3 Hz, 1H), 3.78 - 3.68 (m, 3H), 3.14 - 2.90 (m, 7H), 2.75 - 2.42 (m, 6H), 2.40 - 2.19 (m, 3H), 2.13 - 2.05 (m, 1H), 1.98 (d, J=2.0 Hz, 3H), 1.95 - 1.69 (m, 6H), 1.68 (s, 3H), 1.65 - 1.30 (m, 7H), 1.25 (m, 11H), 1.10 - 1.01 (m, 6H), 0.98 - 0.87 (m, 6H), 0.87 - 0.83 (m, 3H).

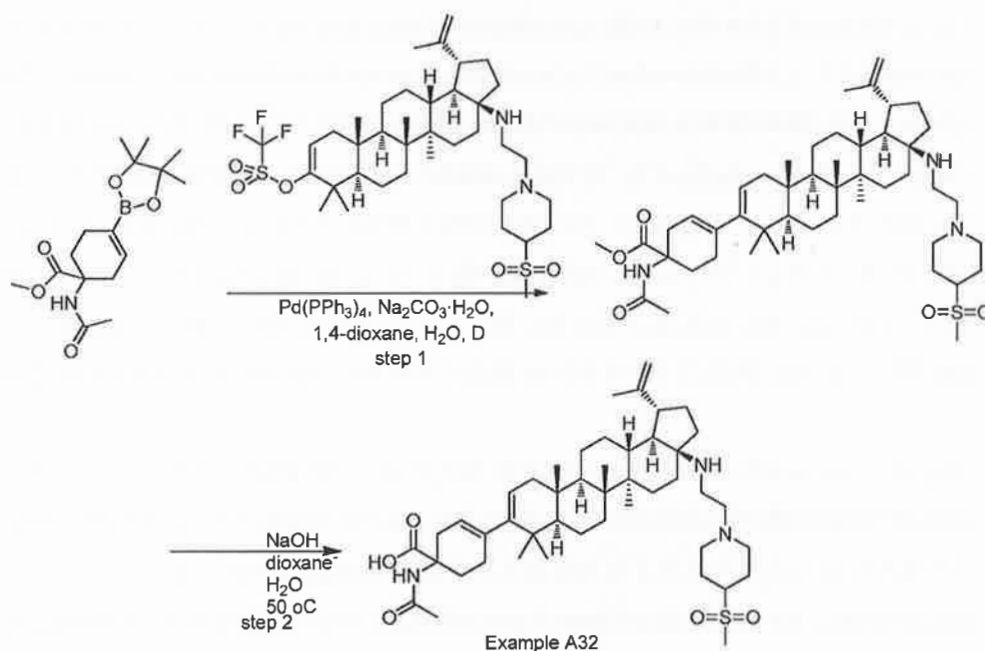
Step 4: 1-acetamido-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the method described in step 3 for the preparation of Example 4, using methyl 1-acetamido-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-

dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-
 2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-
 cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as the reactant. The crude was
 purified by preparative HPLC with method 13 to afford the title compound as a mixture
 of diastereomers in 41.5 % yield. MS: m/e 752.55 ($M+H$)⁺, 2.53 min (method 8). ¹H
 NMR (500MHz, CHLOROFORM-d) δ 6.38 - 6.05 (m, 1H), 5.27 (br. s., 1H), 5.22 (d,
 $J=5.0$ Hz, 1H), 4.73 (br. s., 1H), 4.62 (s, 1H), 3.26 - 2.90 (m, 9H), 2.89 - 2.49 (m, 5H),
 2.46 - 2.23 (m, 3H), 2.22 - 2.06 (m, 4H), 2.00 (m, 2H), 1.97 (s, 3H), 1.90 (d, $J=7.2$ Hz,
 4H), 1.70 (s, 3H), 1.63 - 1.15 (m, 14H), 1.11 (br. s., 3H), 1.03 - 0.97 (m, 6H), 0.94 (br. s.,
 3H), 0.87 (br. s., 3H).

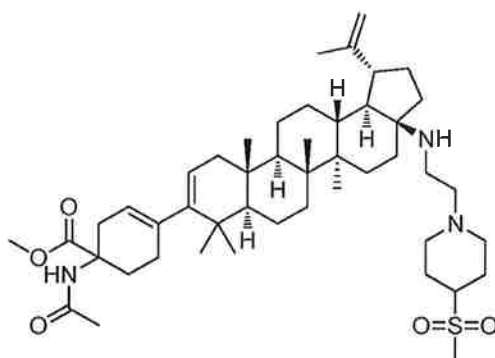
Example A32

**Preparation of 1-acetamido-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-
 5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-
 (prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-
 1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid**



Step 1: Preparation of methyl 1-acetamido-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate



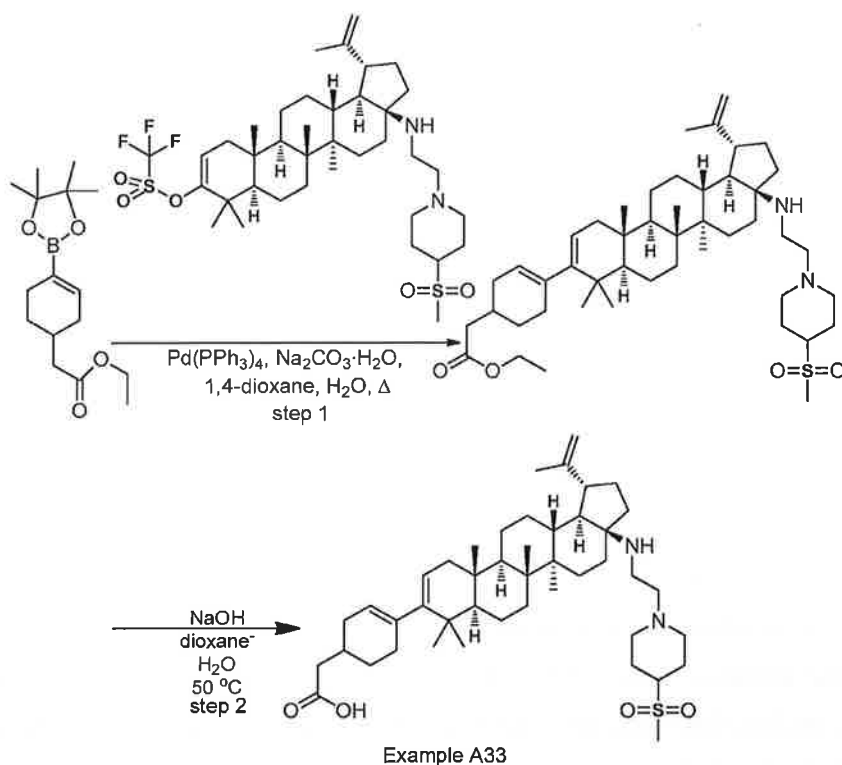
The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (triflate-2) and methyl 1-acetamido-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate as the reactants. The product was obtained as a mixture of diastereomers in 58.3 % yield. MS: m/e 794.6 (M+H)⁺, 2.718 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.71 (d, J=5.5 Hz, 1H), 5.28 (br. s., 1H), 5.22 (s, 1H), 4.73 (br. s., 1H), 4.60 (br. s., 1H), 3.75 (s, 3H), 3.15 (d, J=10.5 Hz, 2H), 2.92 - 2.79 (m, 4H), 2.73 - 2.53 (m, 4H), 2.52 - 2.22 (m, 7H), 2.20 - 2.08 (m, 5H), 2.03 (br. s., 1H), 2.00 (d, J=1.8 Hz, 3H), 1.98 - 1.75 (m, 7H), 1.70 (s, 3H), 1.68 - 1.20 (m, 15H), 1.14 - 1.04 (m, 6H), 1.00 - 0.91 (m, 6H), 0.86 (s, 3H).

Step 2: 1-acetamido-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylic acid was prepared following the

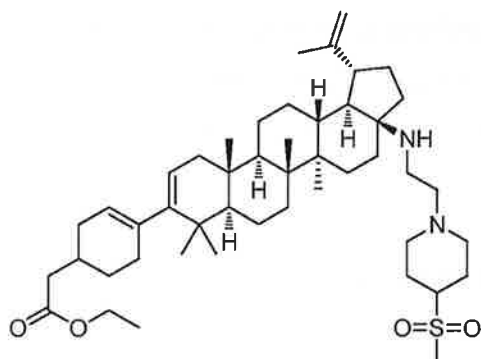
- method described in step 3 for the preparation of Example 4, using methyl 1-acetamido-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as the reactant. The crude was purified by preparative HPLC with method 13 to afford the title compound as a mixture of diastereomers in 41.9 % yield. MS: m/e 780.55 (M+H)⁺, 2.57 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 6.22 (br. s., 1H), 5.36 - 5.24 (m, 1H), 5.21 (br. s., 1H), 4.85 - 4.70 (m, 1H), 4.63 (s, 1H), 3.30 - 3.09 (m, 2H), 2.87 (m, 5H), 2.81 - 2.50 (m, 5H), 2.42 (br. s., 2H), 2.27 - 2.03 (m, 10H), 1.98 (m, 4H), 1.92 (m, 5H), 1.91-1.68 (m, 4H), 1.70 (s, 3H), 1.65 - 1.19 (m, 12H), 1.14 (s, 3H), 1.08 - 0.91 (m, 9H), 0.86 (br. s., 3H).

Example A33

- 15 **Preparation of 2-(4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetic acid**



Step 1: Preparation of ethyl 2-(4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetate



The title compound was prepared following the method described in step 1 for the preparation of Example 1, using (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate and methyl 1-acetamido-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate from as the reactants.

The title compound was obtained as a mixture of diastereomers in 29.3 % yield. MS: m/e 765.55 (M+H)⁺, 3.03 min (method 8). ¹H NMR (500MHz, CHLOROFORM-d) δ 5.30 (s, 1H), 5.20 - 5.16 (m, 1H), 4.72 (d, J=1.8 Hz, 1H), 4.59 (d, J=1.2 Hz, 1H), 4.17 - 4.11 (m, 2H), 3.12 (t, J=11.9 Hz, 2H), 2.87 - 2.78 (m, 1H), 2.83 (s, 3H), 2.70 - 2.55 (m, 3H), 2.52 - 2.43 (m, 2H), 2.32 - 0.94 (m, 40H), 1.69 (s, 3H), 1.07 (s, 3H), 0.97 - 0.91 (m, 6H), 0.96 (s, 3H), 0.85 (s, 3H).

Step 2: 2-(4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-en-1-yl)acetic acid was prepared following the method described in step 3 for the preparation of Example 4, using methyl 1-acetamido-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)cyclohex-3-enecarboxylate as the reactant. The crude was purified by prep HPLC with method 13 to afford the title compound as a mixture of diastereomers in 39.4 % yield MS: m/e 737.55 (M+H)⁺, 2.928 min (method 8). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.31 (s, 1H), 5.17 (d, J=6.3 Hz, 1H), 4.73 (s, 1H), 4.62 (s, 1H), 3.18 (t, J=12.4 Hz, 2H), 2.90 - 2.68 (m, 5H), 2.84 (s, 3H), 2.58 - 2.50 (m, 1H), 2.32 - 1.02 (m, 37H), 1.69 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.98 - 0.90 (m, 6H), 0.85 (s, 3H).

Biology Data for the Examples

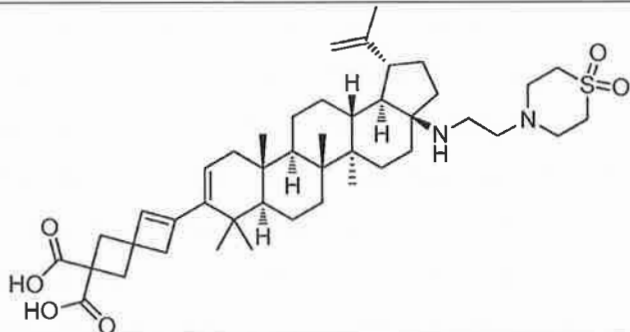
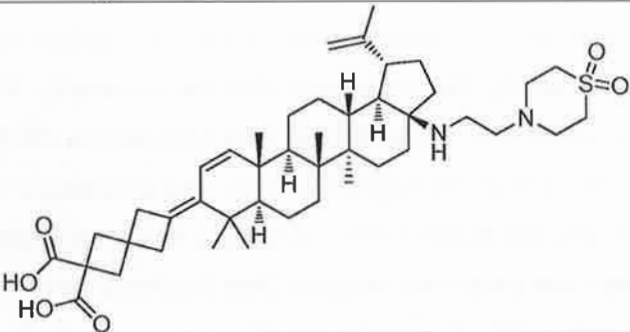
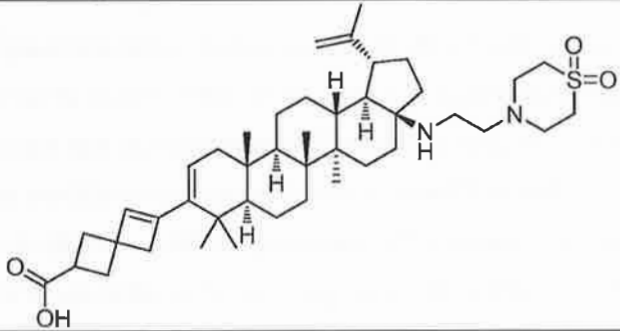
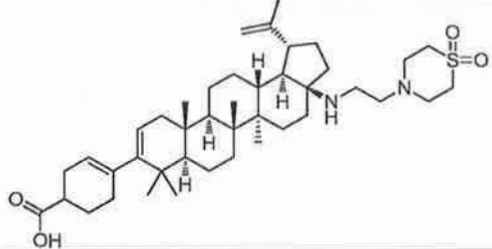
- “μM” means micromolar;
- “mL” means milliliter;
- “μl” means microliter;
- “mg” means milligram;
- “μg” means microgram;

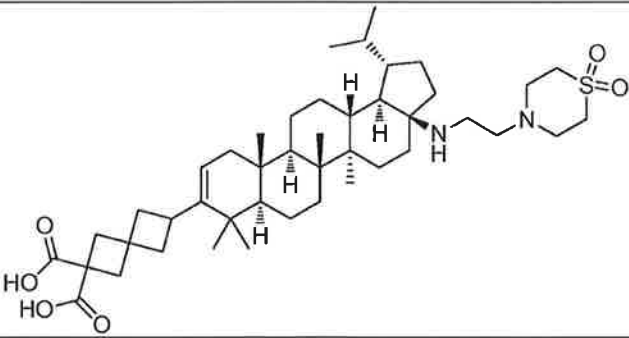
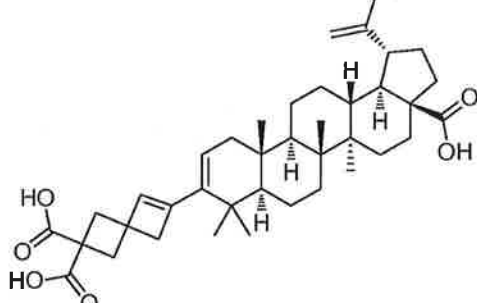
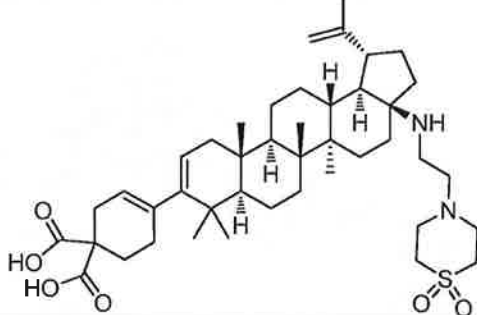
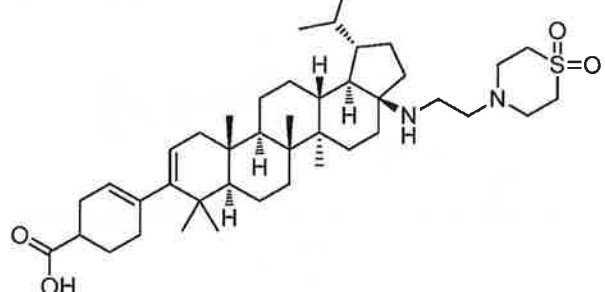
The materials and experimental procedures used to obtain the results reported in Tables 1-2 are described below.

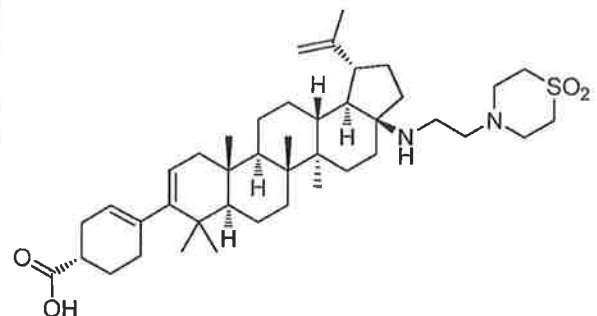
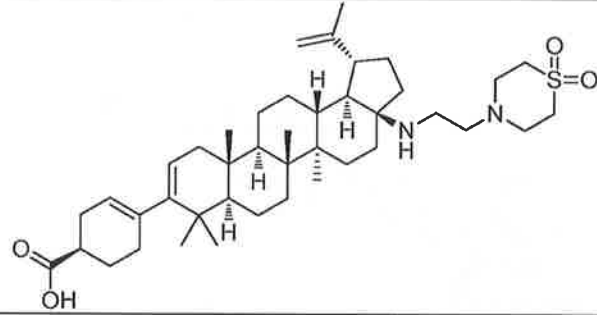
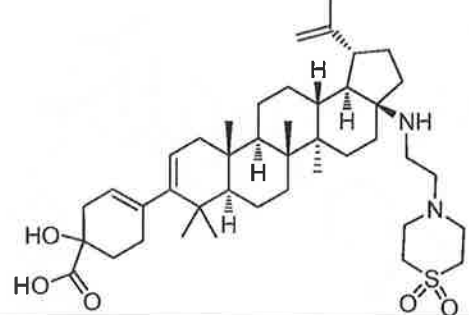
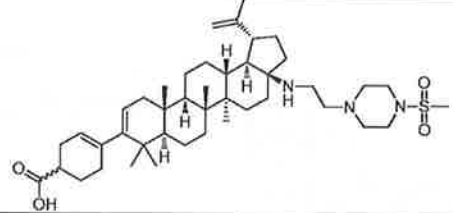
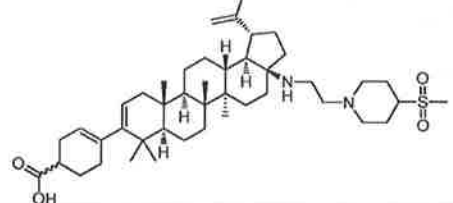
HIV cell culture assay - MT-2 cells and 293T cells were obtained from the NIH AIDS Research and Reference Reagent Program. MT-2 cells were propagated in RPMI 1640 media supplemented with 10% heat inactivated fetal bovine serum, 100 µg/ml penicillin G and up to 100 units/ml streptomycin. The 293T cells were propagated in DMEM media supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 units/ml penicillin G and 100 µg/ml streptomycin. The proviral DNA clone of NL₄₋₃ was obtained from the NIH AIDS Research and Reference Reagent Program. A recombinant NL₄₋₃ virus, in which a section of the nef gene from NL4-3 was replaced with the *Renilla* luciferase gene, was used as a reference virus. In addition, residue Gag P373 was converted to P373S. Briefly, the recombinant virus was prepared by transfection of the altered proviral clone of NL₄₋₃. Transfections were performed in 293T cells using LipofectAMINE PLUS from Invitrogen (Carlsbad, CA), according to manufacturer's instruction. The virus was titered in MT-2 cells using luciferase enzyme activity as a marker. Luciferase was quantitated using the Dual Luciferase kit from Promega (Madison, WI), with modifications to the manufacturer's protocol. The diluted Passive Lysis solution was pre-mixed with the re-suspended Luciferase Assay Reagent and the re-suspended Stop & Glo Substrate (2:1:1 ratio). Fifty (50) µL of the mixture was added to each aspirated well on assay plates and luciferase activity was measured immediately on a Wallac TriLux (Perkin-Elmer). Antiviral activities of inhibitors toward the recombinant virus were quantified by measuring luciferase activity in cells infected for 4-5 days with NLRLuc recombinants in the presence serial dilutions of the inhibitor. The EC₅₀ data for the compounds is shown in Table 1.

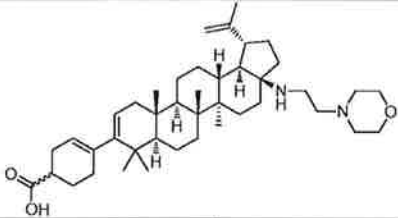
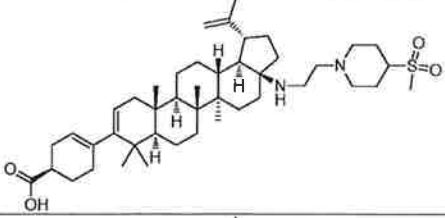
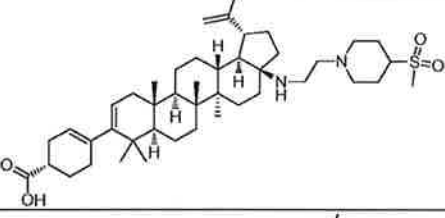
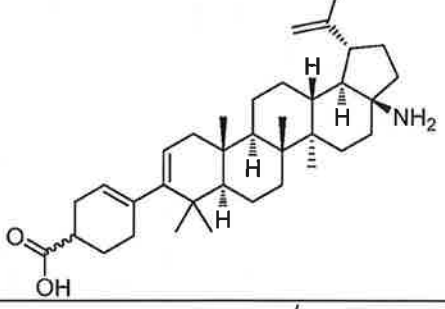
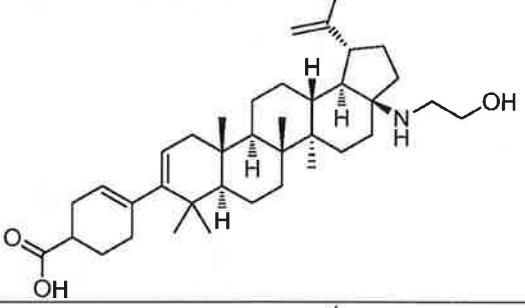
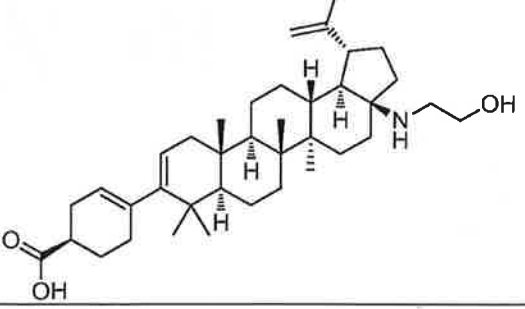
Results

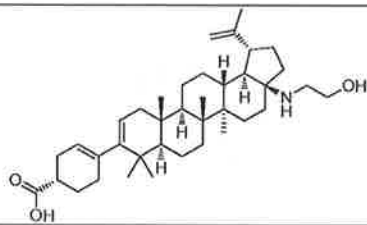
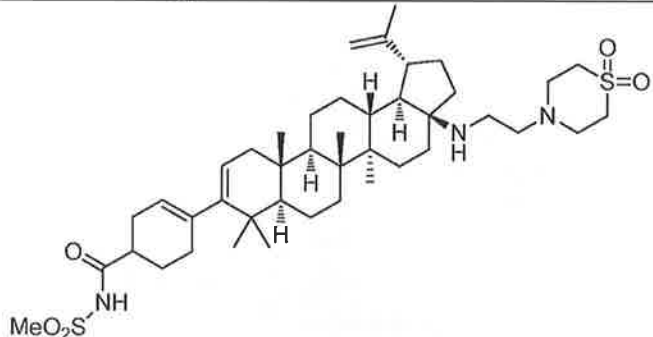
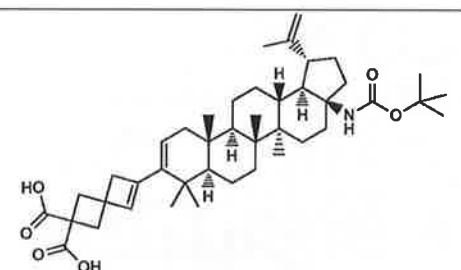
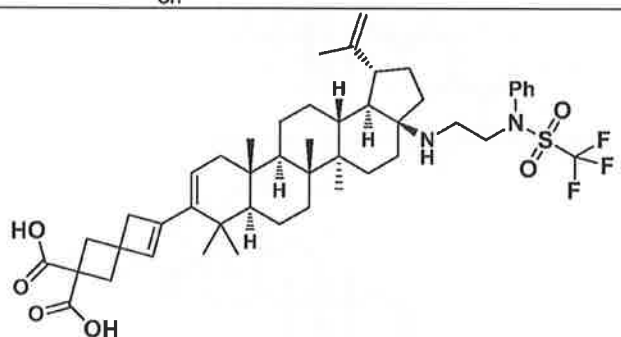
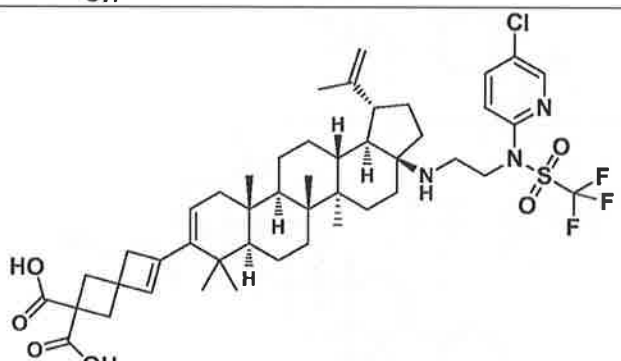
Table 1

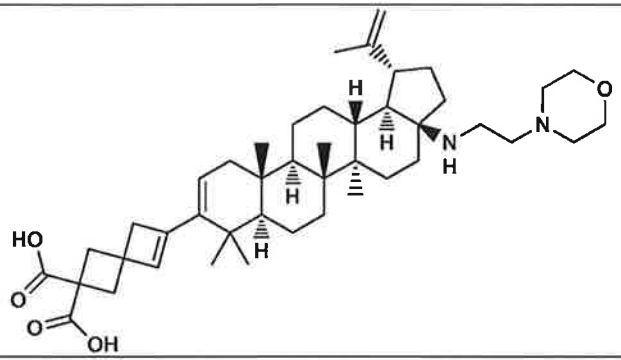
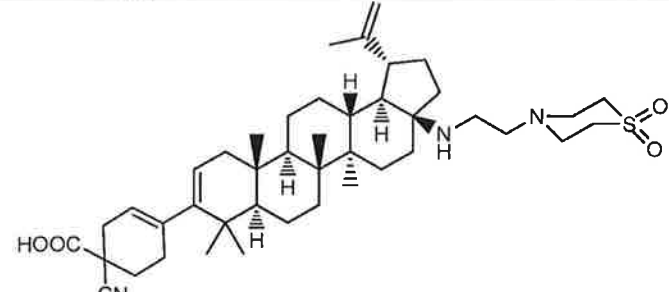
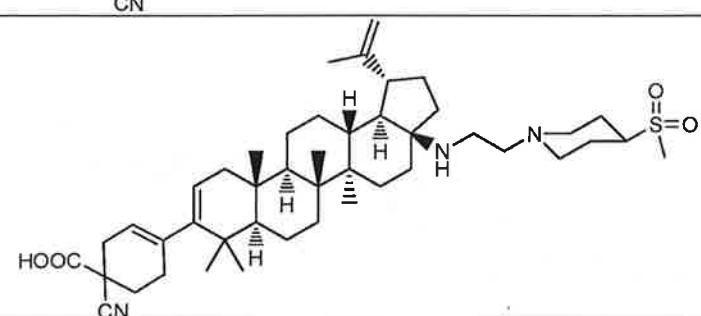
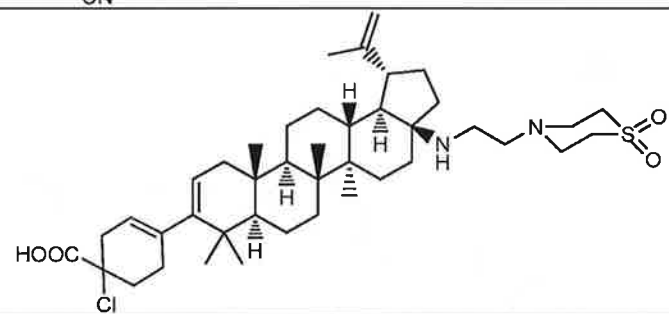
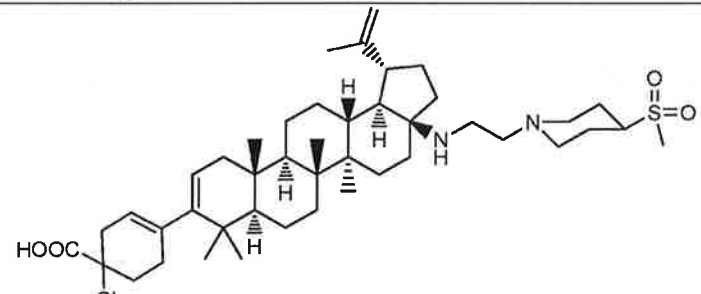
Example #	Structure	EC ₅₀ (μM)
1		0.01
2		0.03
3		1.54E-03
4		6.59E-04

5		0.04
6		0.03
7		0.10
8		1.01E-03

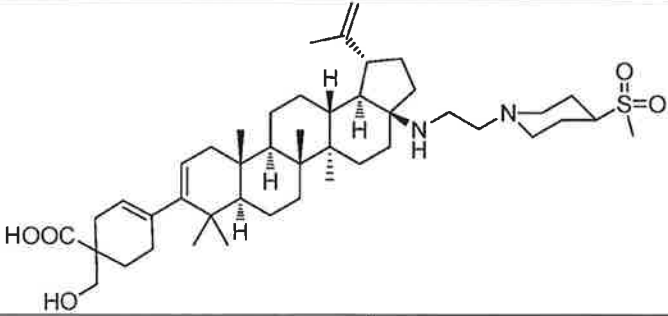
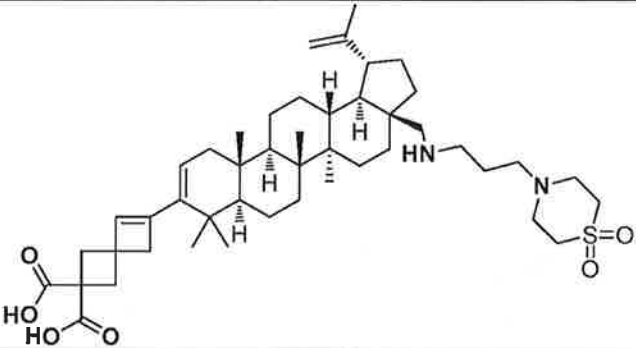
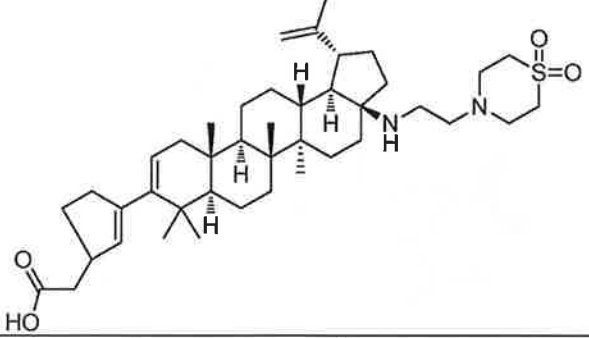
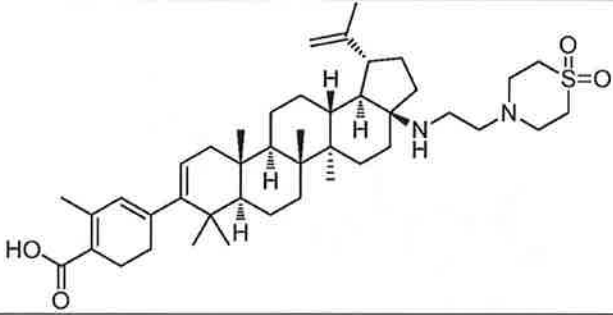
9		8.92E-04
10		1.26E-03
11		1.99E-03
12		3.03E-03
13		9.75E-04

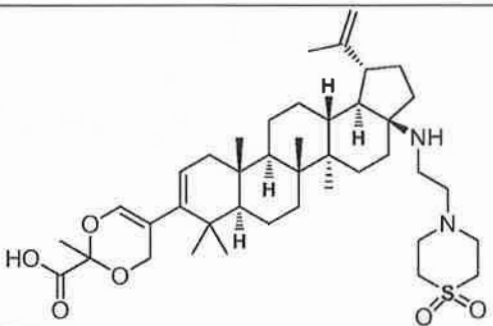
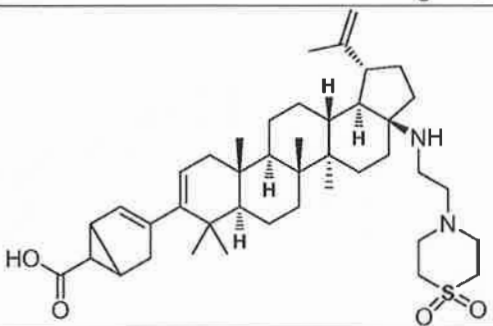
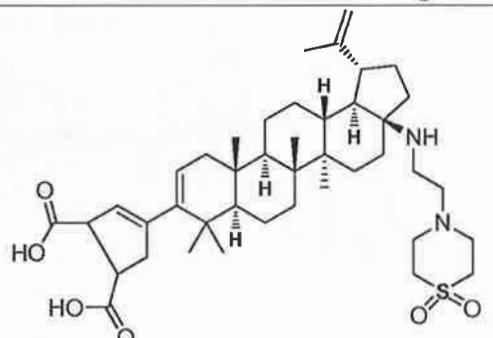
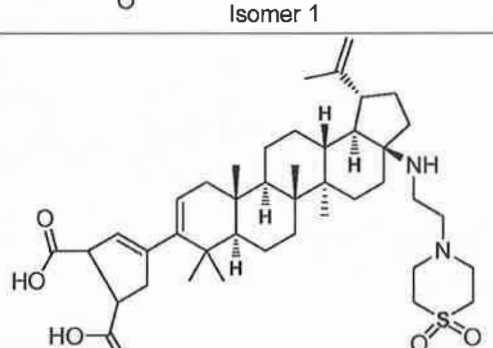
14		5.61E-03
15		1.36E-03
16		3.05E-03
17		8.77E-04
18		1.38E-03
19		1.14E-03

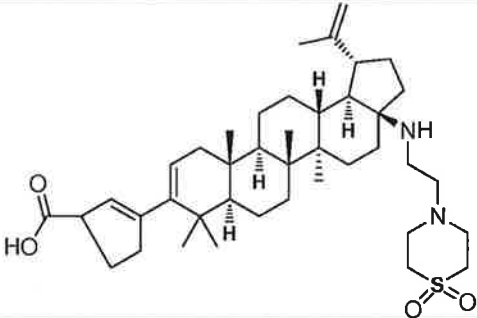
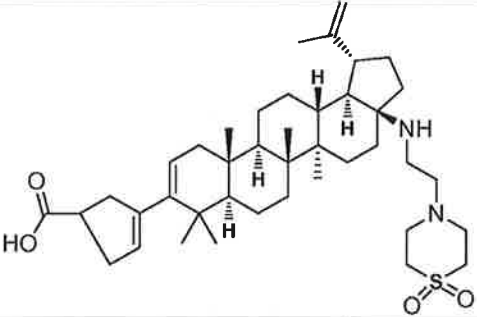
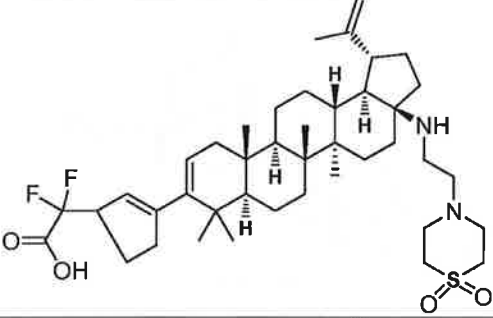
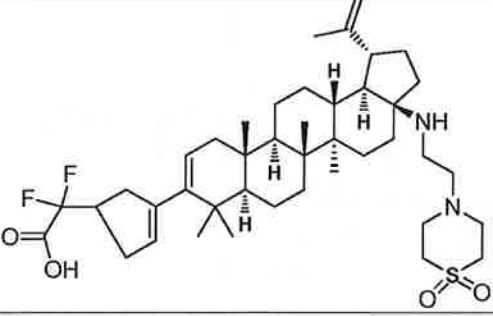
20		1.57E-03
21		1.80E-03
A1		0.57
A2		1.07
A3		1.75

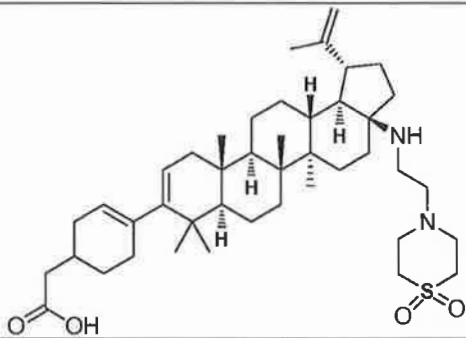
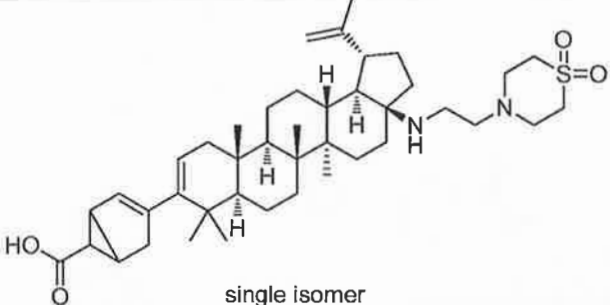
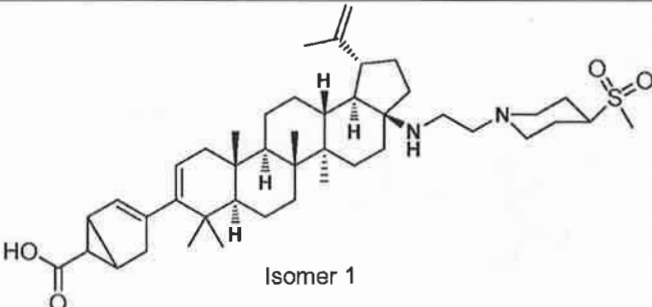
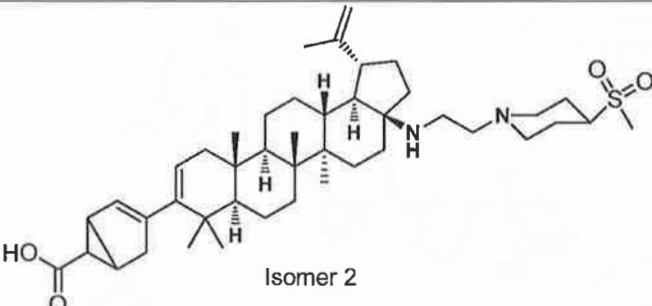
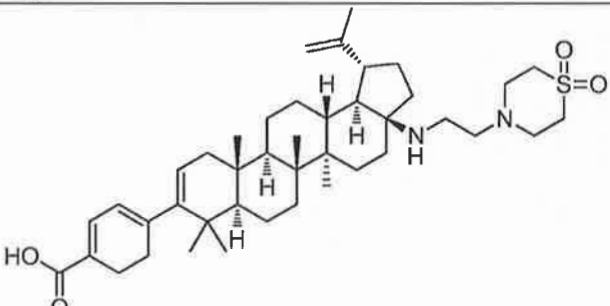
A4		0.10
A5		4.26E-03
A6		6.18E-03
A7		2.91E-03
A8		2.42E-03

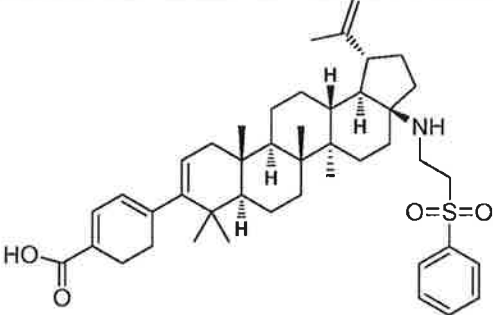
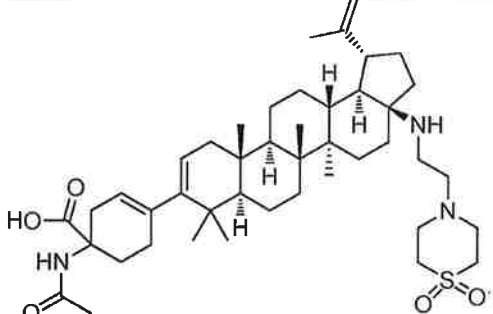
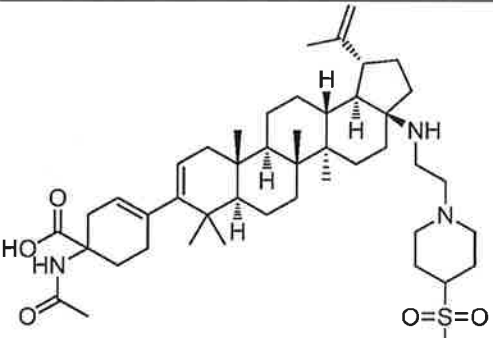
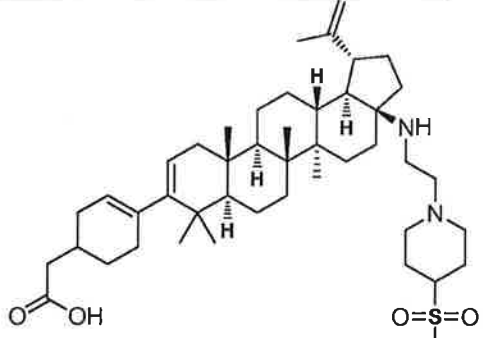
[illegible]

A13		3.01E-04
A14		0.19
A15		5.47E-04
A16		2.23E-03

A17		0.32
A18		2.26E-03
A19	 Isomer 1	0.10
A20	 Isomer 2	0.06

A21		2.76E-03
A22		3.53E-03
A23		5.63E-03
A24		4.65E-03

A25		1.31E-03
A26	 single isomer	9.41E-04
A27	 Isomer 1	9.21E-04
A28	 Isomer 2	6.58E-04
A29		1.37E-03

A30		0.09
A31		0.01
A32		1.50E-03
A33		0.57

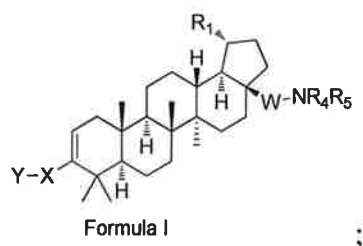
The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the following examples and the foregoing

description. Such modifications are also intended to fall within the scope of the appended claims.

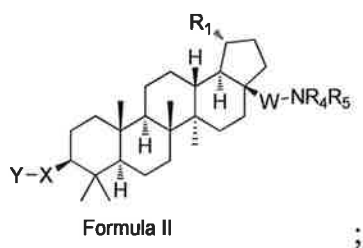
What is claimed is:

1. A compound, which is selected from the group consisting of:

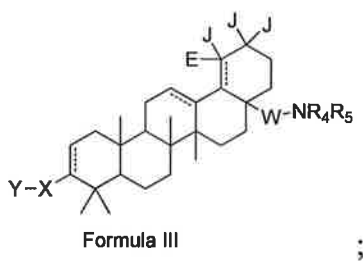
a compound of formula I



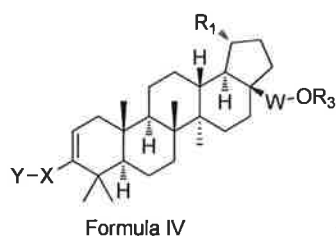
a compound of formula II



a compound of formula III



and a compound of formula IV

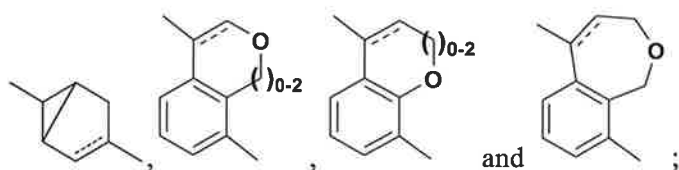


wherein R_1 is isopropenyl or isopropyl;

J and E are independently $-H$ or $-CH_3$, and E is absent when the double bond is present;

X is selected from the group of C_{4-8} cycloalkyl, C_{4-8} cycloalkenyl, C_{4-9} spirocycloalkyl, C_{4-9} spirocycloalkenyl, C_{4-8} oxacycloalkyl, C_{4-8} dioxacycloalkyl, C_{6-8} oxacycloalkenyl, C_{6-8} dioxacycloalkenyl, C_6 cyclodialkenyl, C_6 oxacyclodialkenyl, C_{6-9} oxaspirocycloalkyl and C_{6-9} oxaspirocycloalkenyl ring, wherein X is substituted with A, wherein A is at least one member selected from the group of $-H$, $-halo$, $-hydroxyl$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkyl-Q, $-alkylsubstituted\ C_{1-6}\ alkyl-Q$, $-CN$, $-CF_2Q$, $-NR_8R_9$, $-COOR_2$ and $-CONR_2R_2$;

X is also selected from the group of:



wherein Q is selected from the group of aryl, heteroaryl, substituted heteroaryl, $-OR_2$, $-COOR_3$, $-NR_2R_2$, $-SO_2R_7$, $-CONHSO_2R_3$, and $-CONHSO_2NR_2R_2$;

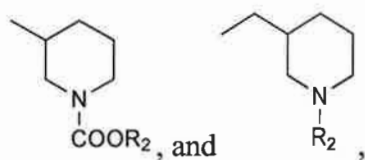
R_2 is $-H$, $-C_{1-6}$ alkyl, $-alkylsubstituted\ C_{1-6}\ alkyl$ or $-arylsubstituted\ C_{1-6}\ alkyl$;

Y is selected from the group of $-COOR_2$, $-C(O)NR_2SO_2R_3$, $-C(O)NHSO_2NR_2R_2$, $-NR_2SO_2R_2$, $-SO_2NR_2R_2$, $-C_{3-6}$ cycloalkyl- $COOR_2$, $-C_{2-6}$ alkenyl- $COOR_2$, $-C_{2-6}$ alkynyl- $COOR_2$, $-C_{1-6}$ alkyl- $COOR_2$, $-alkylsubstituted\ C_{1-6}\ alkyl$, $-COOR_2$, CF_2-COOR_2 , $-NHC(O)(CH_2)_n-COOR_2$, $-SO_2NR_2C(O)R_2$, tetrazole, and $-CONHOH$, wherein $n=1-6$;

W is absent, CH₂ or CO;

R₃ is -C₁₋₆ alkyl or -alkylsubstituted C₁₋₆ alkyl;

R₄ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-C(OR₃)₂-C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-Q₁, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₁, aryl, heteroaryl, substituted heteroaryl, -COR₆, -COCOR₆, -SO₂R₇, -SO₂NR₂R₂,



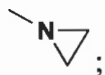
with the proviso that R₄ or R₅ cannot be COR₆ or COCOR₆ when W is CO;

wherein Q₁ is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₁₀R₁₁ and -SO₂R₇;

R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₁₀, -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

with the proviso that only one of R₄ or R₅ can be selected from the group of -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

or when W is absent or is CH₂, then R₄ and R₅ can be taken together with the adjacent N to form

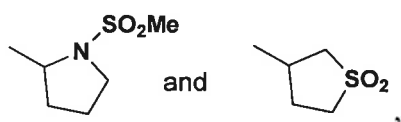


R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

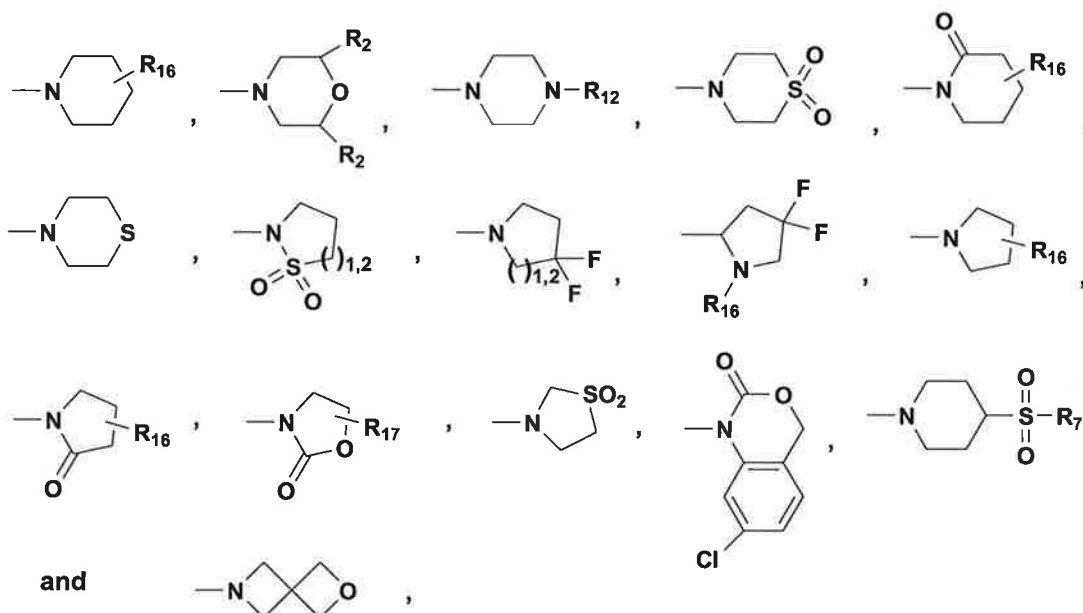
wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

R₇ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -CF₃, aryl, and heteroaryl;

R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,
and R₈ and R₉ are also independently selected from the group of



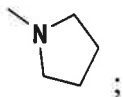
or R₈ and R₉ are taken together with the adjacent N to form a cycle selected from the group of:



with the proviso that only one of R₈ or R₉ is -COOR₃;

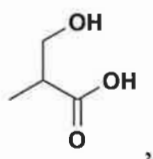
R₁₀ and R₁₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl and -C₃₋₆ cycloalkyl,

or R₁₀ and R₁₁ are taken together with the adjacent N to form the cycle

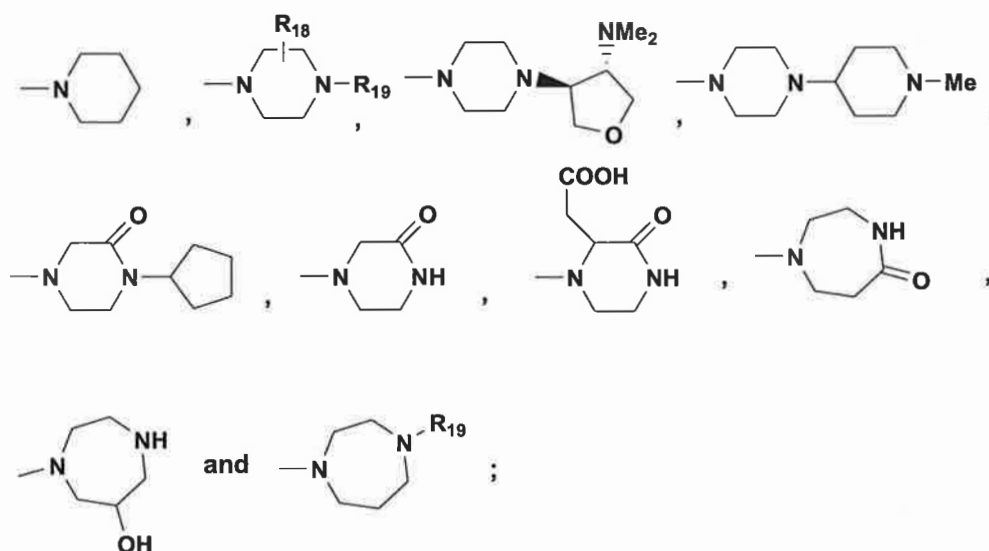


R₁₂ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ alkyl-OH; -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -COR₇, -COONR₂₂R₂₃, -SOR₇, and -SONR₂₄R₂₅;

R₁₃ and R₁₄ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃, C₁₋₆ substituted alkyl-Q₃ and



or R₁₃ and R₁₄ are taken together with the adjacent N to form a cycle selected from the group of:



Q₃ is selected from the group of heteroaryl, substituted heteroaryl, -NR₂₀R₂₁, -CONR₂R₂, -COOR₂, -OR₂, and -SO₂R₃;

R₁₅ is selected from the group of -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃ and -C₁₋₆ substituted alkyl-Q₃;

R₁₆ is selected from the group of -H, -C₁₋₆ alkyl, -NR₂R₂, and -COOR₃;

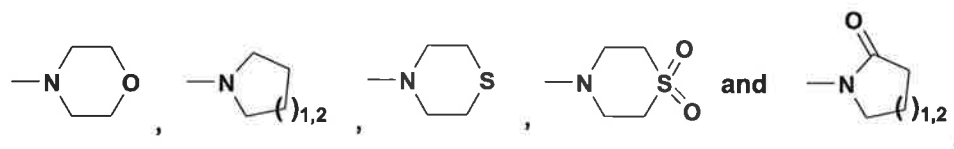
R₁₇ is selected from the group of -H, -C₁₋₆ alkyl, -COOR₃, and aryl;

R₁₈ is selected from the group of -COOR₂ and -C₁₋₆ alkyl-COOR₂;

R₁₉ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₄, -COR₃, -COOR₃,
wherein Q₄ is selected from the group of -NR₂R₂ and -OR₂;

R₂₀ and R₂₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ substituted alkyl-OR₂, and -COR₃,

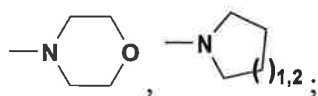
or R₂₀ and R₂₁ are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R₂₀ or R₂₁ is -COR₃;

R₂₂ and R₂₃ are independently selected from the group of H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, and -C₁₋₆ cycloalkyl,

or R₂₂ and R₂₃ are taken together with the adjacent N to form a cycle selected from the group of



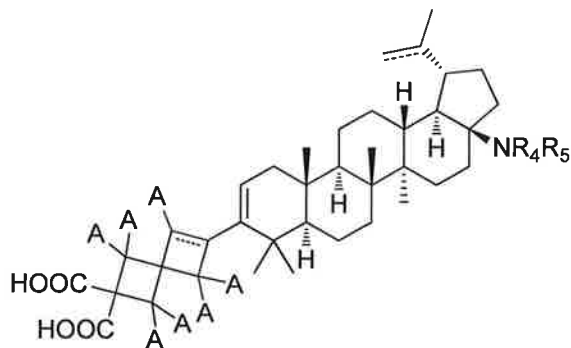
R₂₄ and R₂₅ are independently from the group of H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₅, -C₁₋₆ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

and Q₅ is selected from the group of halogen and SO₂R₃;

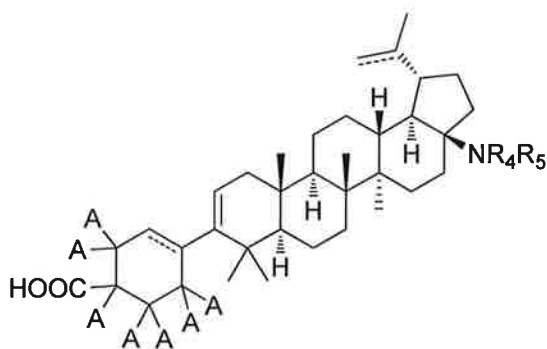
and pharmaceutically acceptable salts thereof.

2. The compound as claimed in claim 1, wherein said compound is a compound of Formula I.
3. The compound as claimed in claim 1, wherein said compound is a compound of Formula II.
4. The compound as claimed in claim 1, wherein said compound is a compound of Formula III.
5. The compound as claimed in claim 2, wherein R₁ is isopropenyl.
6. The compound as claimed in claim 5, wherein X is selected from the group of C₄₋₈ cycloalkenyl, C₄₋₉ spirocycloalkyl, and C₄₋₉ spirocycloalkenyl.

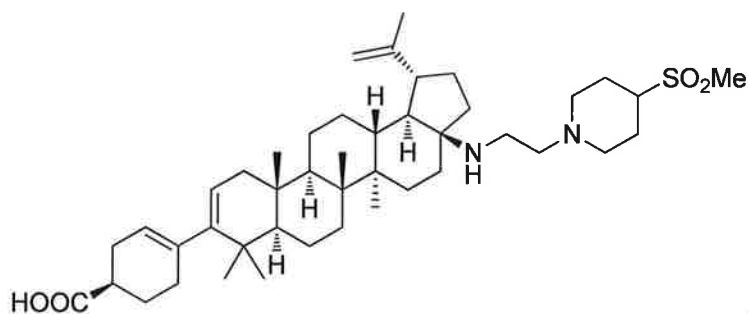
7. The compound as claimed in claim 6, wherein Y is $-\text{COOR}_2$.
8. The compound as claimed in claim 7, wherein Y is $-\text{COOH}$.
9. The compound as claimed in claim 6, wherein A is $-\text{H}$.
10. The compound as claimed in claim 2, wherein said compound is a compound with the following general structure selected from the group of:

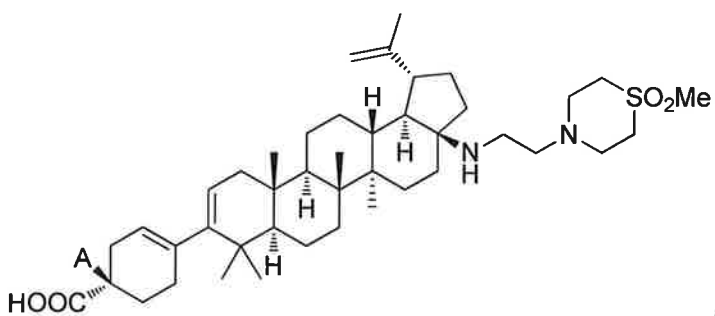
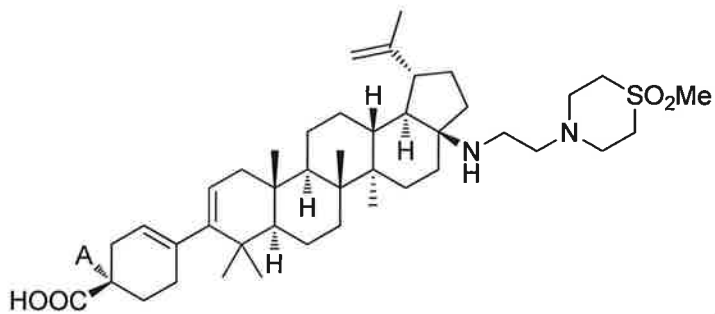
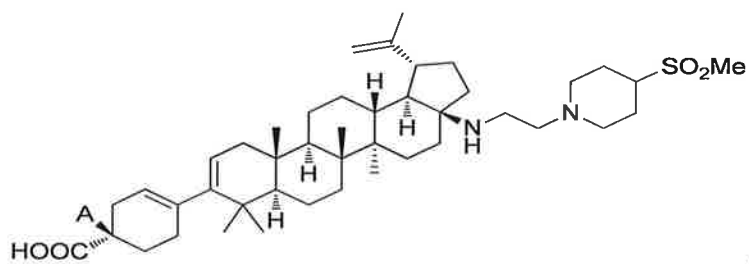
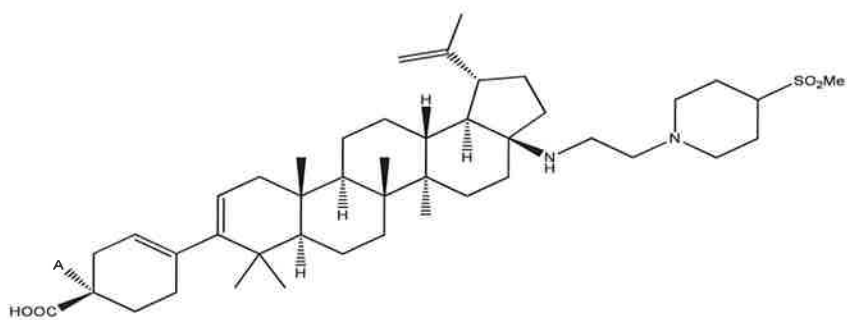
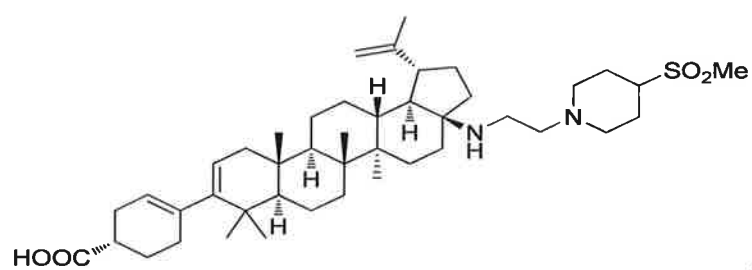


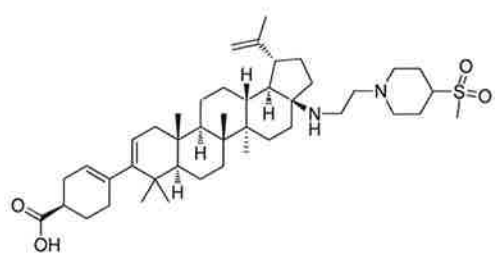
and



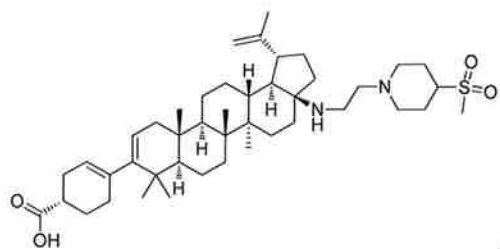
11. A compound, which is selected from the group consisting of:



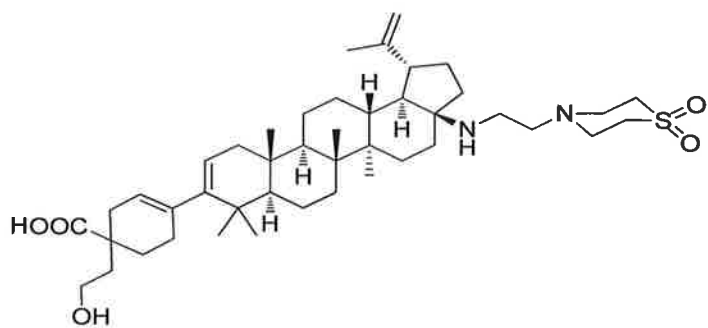




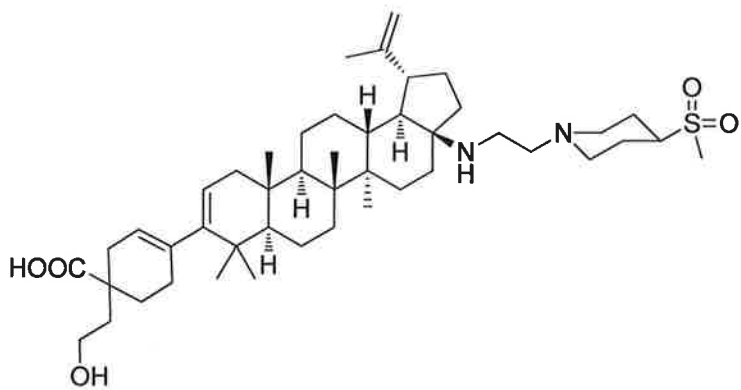
,



,

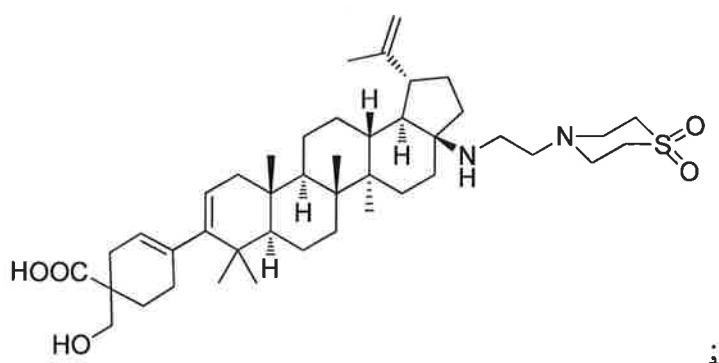


,



,

and



and pharmaceutically acceptable salts thereof.

12. A pharmaceutical composition which comprises an HIV ameliorating amount of one or more of the compounds as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

13. A pharmaceutical composition which comprises an HIV ameliorating amount of one or more of the compounds as claimed in claim 10, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

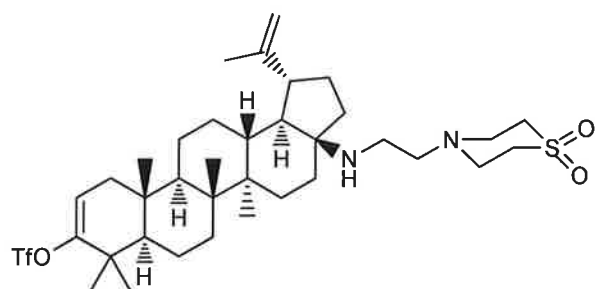
14. A pharmaceutical composition which comprises an HIV ameliorating amount of one or more of the compounds as claimed in claim 11, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

15. The pharmaceutical composition of claim 12, useful for treating infection by HIV, which additionally comprises an HIV ameliorating amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) another HIV entry inhibitor.

16. The compound as claimed in claim 1, wherein W is absent.

17. The compound as claimed in claim 1, wherein said compound is a compound of Formula IV.

18. The intermediate compound which is selected from the group of



and

