



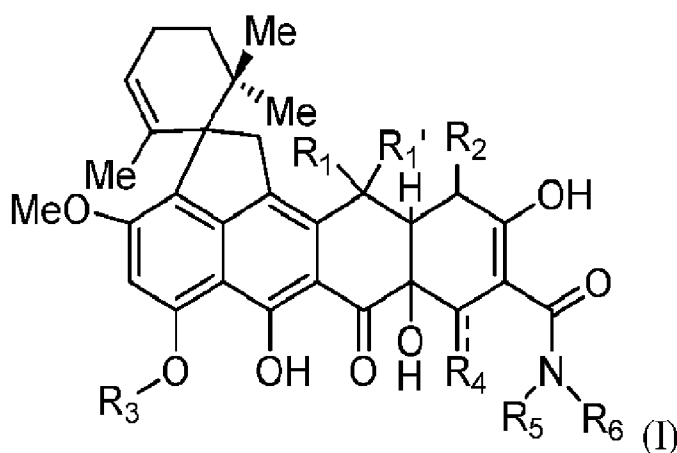
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(54) **Title:** ENANTIOENRICHED VIRIDICATUMTOXIN B ANALOGS

(57) **Abstract:** In one aspect, the present disclosure provides derivatives of viridicatumtoxin of the formula wherein the variables are as defined herein. Also provided herein are compositions and methods of treating a bacterial infection, a viral infection, or in the treatment of cancer. The present disclosure also provides methods of synthesizing enantiopure viridicatumtoxin and other anthrone compounds.

DESCRIPTION

ENANTIOENRICHED VIRIDICATUMTOXIN B ANALOGS

This application claims the benefit of priority to U.S. Provisional Application Serial No. 62/322,935, filed on April 15, 2016, the entire contents of which are hereby incorporated by reference.

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BACKGROUND

This invention was made with government support under Grant Number AI055475 awarded by the National Institutes of Health. The government has certain rights in the invention.

1. Field

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This disclosure relates to the fields of medicine, pharmacology, chemistry, antimicrobial activity, and oncology. In particular, new compounds, compositions, methods of treatment, and methods of synthesis relating to viridicatumtoxin and derivatives thereof are disclosed.

2. Related Art

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Since the discovery of chlortetracycline (**4**; **FIG. 1A**) in the late 1940's, tetracycline antibiotics such as chlortetracycline (**4**), oxytetracycline (**5**), and tetracycline (**6**) have been commonly prescribed to treat bacterial infections (Duggar, 1948). Throughout the years, as bacterial resistance grew or improved therapeutic properties were needed, additional therapeutic agents including second generation tetracycline derivatives such as minocycline (**7**) and doxycycline (**8**) and third generation tetracycline derivatives such as tigecycline (**9**) and eravacycline (TP-434, **10**) have been developed (**FIG. 1A**) (Tally, *et al.*, 1995; Sutcliffe, *et al.*, 2013; Chopra and Roberts, 2001).

20

Since the discovery of the commercial importance of these molecules for the biological activity, many efforts have been undertaken to synthesize tetracycline derivatives including recent efforts by the Myers (Charest, *et al.*, 2005; Charest, *et al.*, 2005; Brubaker and Myers, 2007; Sun, *et al.*, 2008; Kummer, *et al.*, 2011; Wright and Myers, 2011) and Evans groups (Wzorek, *et al.*, 2012). While there have been many attempts to prepare these compounds, new and improved methods resulting in enantiopure anthrones such as those contained in viridicatumtoxin B are still in demand.

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In 2008, Kim, *et al.*, isolated viridicatumtoxin B (**1**) from *Penicillium* sp. FR11 along with viridicatumtoxin A (**2**). This compound was investigated through NMR spectroscopy and assigned the structure **1'** but this original structure has been revised based upon further analysis and after the total synthesis of viridicatumtoxin B (Nicolau, *et al.*, 2013). These compounds have been shown to have potent antibacterial properties in a number of bacterial strains including both Gram-positive and Gram-negative bacteria (Kim, *et al.*, 2008). Without being bound by theory, further study and analysis suggests that the viridicatumtoxin's antibacterial properties arise not by binding to the 30S subunit of the ribosome like many tetracycline compounds but by inhibiting UPP synthase, an enzyme associated with bacterial peptidoglycan biosynthesis (Inokoshi, *et al.*, 2013; Koyama, *et al.*, 2013). Furthermore, viridicatumtoxin A (**2**) shows promising anticancer

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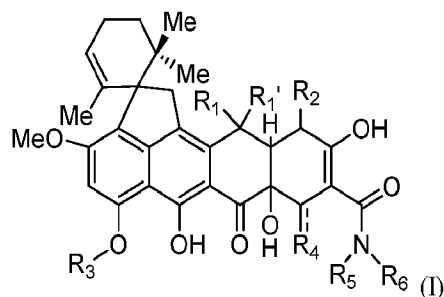
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activity against a selection of cancer cell lines (NIH Results of Viridicatumtoxin A NCI 60 Cell line assay) as well as shows antiviral activity (WO 2009/008906).

As such, new analogs of viridicatumtoxin could provide access to a more efficacious antimicrobial or cancer drug and new methods of their synthesis could allow cost effective clinical access to these compound for use in the treatment of microbial infections and as chemotherapeutic agents.

SUMMARY

Thus, in accordance with the present disclosure, there is provided a compound of the formula:



wherein:

R_1 and $R_{1'}$ are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and $R_{1'}$ are taken together and are oxo;

R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is hydrogen or a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

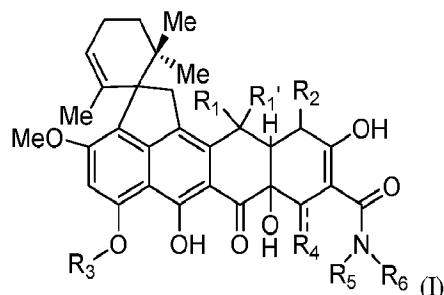
R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

provided that when R_2 is hydrogen and R_3 is hydrogen or methyl, then R_1 is not methoxy or R_1 and $R_{1'}$ are not oxo;

or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds are further defined as:



wherein:

R_1 and $R_{1'}$ are each independently alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8);

5 R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is hydrogen or a group of the formula: $-Y-R_7$, wherein:

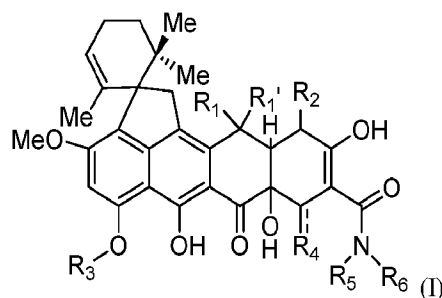
Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

10 R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds are further defined as:



15 wherein:

R_1 and $R_{1'}$ are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and $R_{1'}$ are taken together and are oxo;

R_2 is amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

20 R_3 is hydrogen or a group of the formula: $-Y-R_7$, wherein:

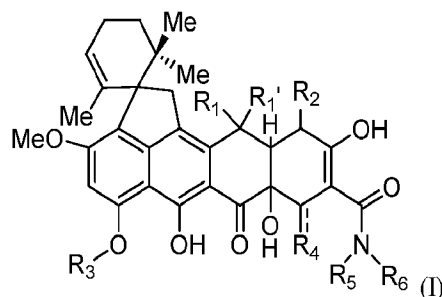
Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

25 R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds are further defined as:



wherein:

R_1 and $R_{1'}$ are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and $R_{1'}$ are taken together and are oxo;

5 R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

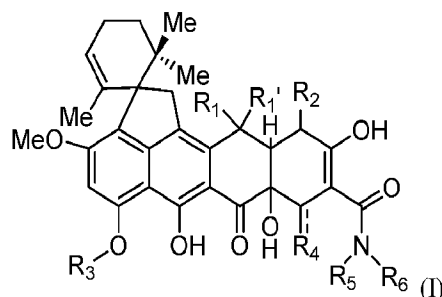
10 R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

provided that when R_2 is hydrogen and R_3 is methyl, then R_1 is not methoxy or R_1 and $R_{1'}$ are not oxo;

15 or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds are further defined as:



wherein:

R_1 and $R_{1'}$ are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and $R_{1'}$ are taken together and are oxo;

20 R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

25 R_7 is amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R₄ is hydroxy, oxo, alkoxy_(C<8), or substituted alkoxy_(C<8); and

R₅ and R₆ are each independently hydrogen, alkyl_(C<8), or substituted alkyl_(C<8);

or a pharmaceutically acceptable salt thereof.

In some embodiments, R₁ and R₁' are taken together and are oxo. In some embodiments, R₁ is alkoxy_(C≤6) or substituted alkoxy_(C≤6). In other embodiments, R₁ is hydrogen. In some embodiments, R₁' is alkoxy_(C≤6) or substituted alkoxy_(C≤6). In other embodiments, R₁' is hydrogen. In some embodiments, R₂ is hydrogen. In some embodiments, R₂ is dialkylamino_(C≤8) or substituted dialkylamino_(C≤8).

In some embodiments, R₃ is hydrogen. In other embodiments, R₃ is -Y-R₇, wherein:

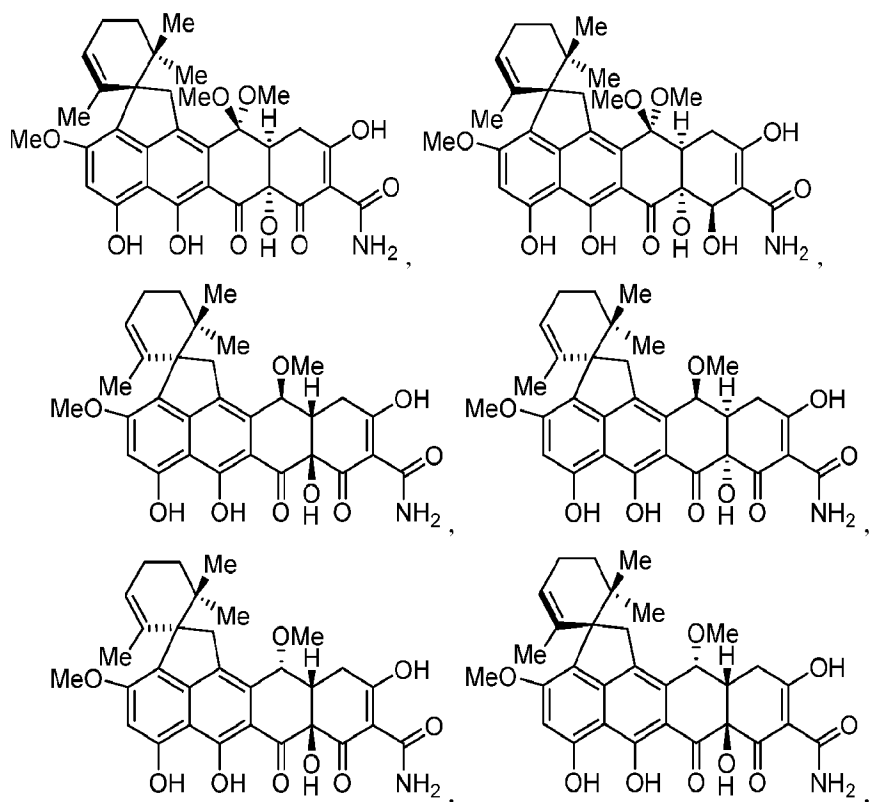
Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

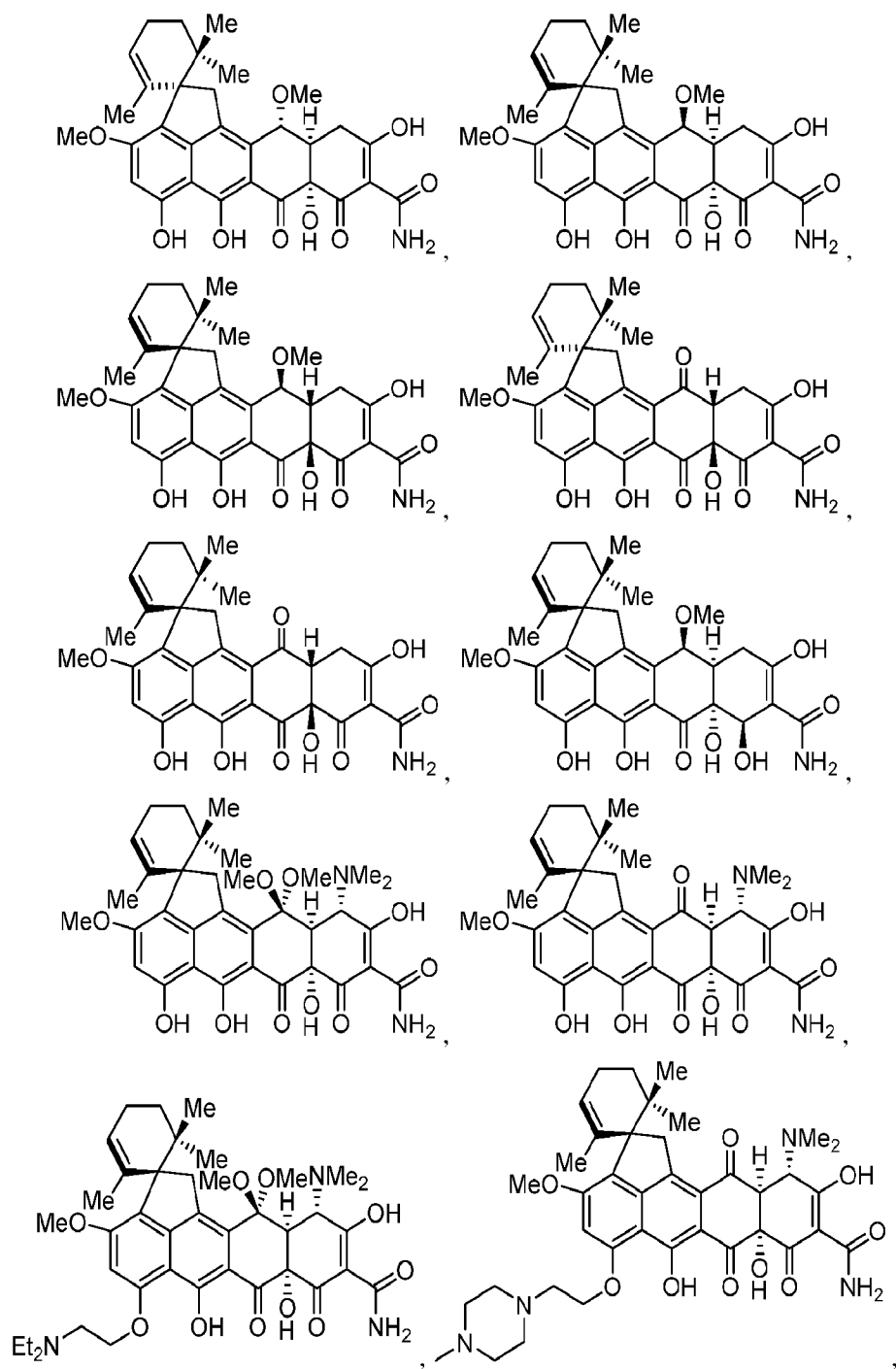
10 R₇ is amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12).

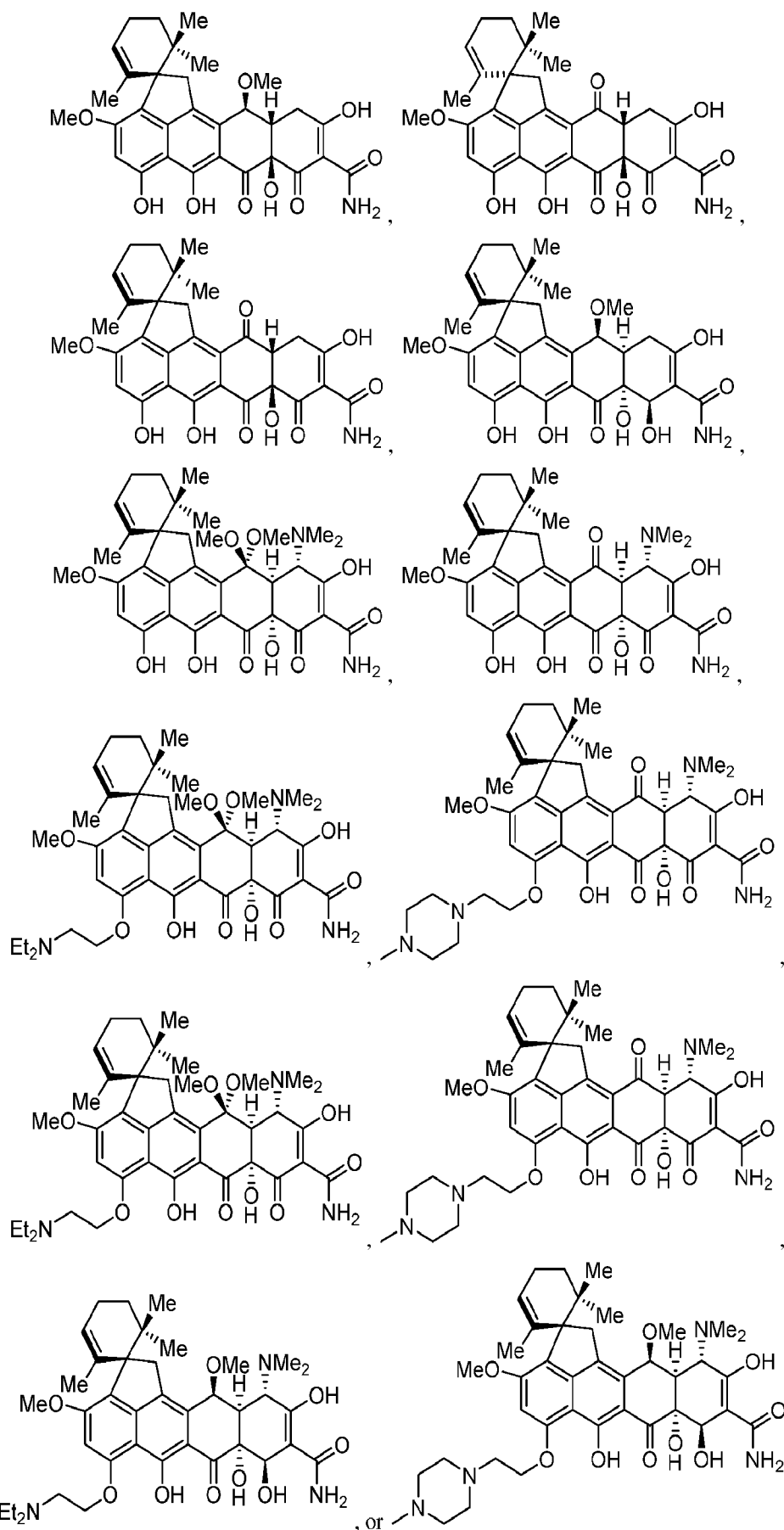
In some embodiments, Y is alkanediyl_(C≤6) or substituted alkanediyl_(C≤6). In some embodiments, R₇ is dialkylamino_(C≤12) or substituted dialkylamino_(C≤12). In other embodiments, R₇ is heterocycloalkyl_(C≤12) or substituted heterocycloalkyl_(C≤12).

15 In some embodiments, R₄ is hydroxy. In other embodiments, R₄ is oxo. In some embodiments, R₅ is hydrogen. In some embodiments, R₆ is hydrogen.

In some embodiments, the compound is present as greater than 80% of a single stereoisomer. In some embodiments, the compound is present as greater than 90% of a single stereoisomer. In some embodiments, the compound is present as greater than 95% of a single stereoisomer. In some embodiments, the compounds are further defined as:

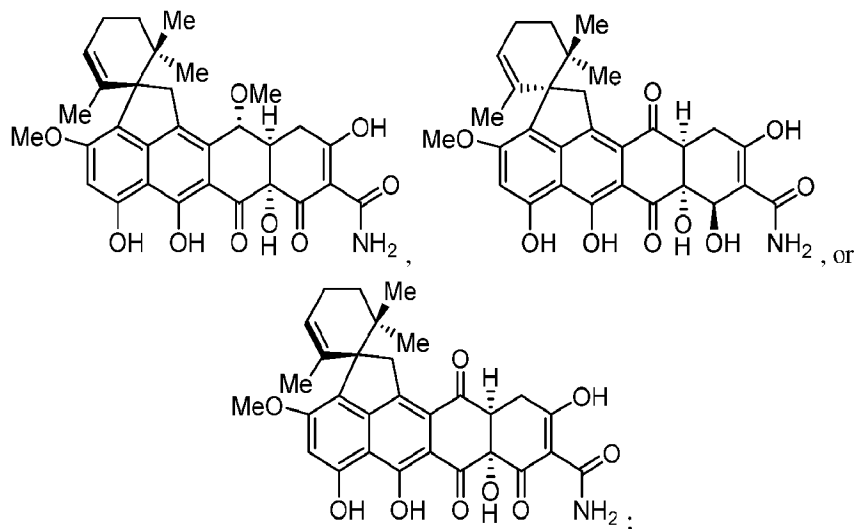






or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure provides compounds of the formula:



or a pharmaceutically acceptable salt thereof;

- 5 wherein the compound is enantiomerically enriched such that the compound is present as at least 80% of the depicted stereoisomer.

In some embodiments, the compound is present as at least 90% of the depicted stereoisomer. In some embodiments, the compound is present as at least 95% of the depicted stereoisomer.

In still yet another aspect, the present disclosure provides pharmaceutical compositions comprising:

- 10 (A) a compound described herein; and
- (B) an excipient.

In some embodiments, the pharmaceutical compositions are formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion. In some embodiments, the pharmaceutical compositions are formulated as a unit dose.

20 In yet another aspect, the present disclosure provides methods of treating a disease or disorder comprising administering a pharmaceutically effective amount of a compound or composition described herein.

In some embodiments, the disease or disorder is a microbial infection such as a bacterial infection. In some embodiments, the infection is by a Gram-positive or Gram-negative bacteria. In some embodiments, the disease is a bacteria infection by *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Escherichia coli*, *Acinetobacter calcoaceticus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Candida albicans*, *Salmonella typhimurium*, *Streptococcus pneumoniae*, *Micrococcus luteus*, *Bacillus cerues*, or *Bacillus subtilis*. In some embodiments, the disease is a bacterial infection by *Staphylococcus aureus* 503, *Staphylococcus aureus* 209, *Staphylococcus aureus* RN420,

methicillin-resistant *Staphylococcus aureus* CCARM 3167, methicillin-resistant *Staphylococcus aureus* 371, methicillin-resistant *Staphylococcus aureus* CCARM 3506, quinolone-resistant *Staphylococcus aureus* CCARM 3505, quinolone-resistant *Staphylococcus aureus* CCARM 3519, *Bacillus subtilis* KCTC 1021, *Bacillus cerues* KCTC 1661, *Micrococcus luteus* KCTC 1056, *Streptococcus pneumoniae* KCTC 3932, 5 *Streptococcus pneumoniae* KCTC 5412, *Enterococcus faecium* 501, *Enterococcus faecium* KCTC 3122, *Enterococcus faecalis* 5613, *Enterococcus faecalis* KCTC 5191, *Enterococcus faecalis* KCTC 3511, *Staphylococcus epidermidis* KCTC 3958, *Salmonella typhimurium* KCTC 1926, *Acinetobacter calcoaceticus* KCTC 2357, *Escherichia coli* CCARM 1358, *Escherichia coli* KCTC 1682, *Pseudomonas aeruginosa* KCTC 2004, *Pseudomonas aeruginosa* KCTC 2742, *Klebsiella aerogenes* KCTC 2619, *Acinetobacter baumannii* 10 AB210, or *Candida albicans* KCTC 7535. In some embodiments, the bacteria is a drug-resistant bacteria.

In some embodiments, the methods further comprise administering a second therapeutic agent such as an antibiotic. In some embodiments, the second therapeutic agent is a tetracycline antibiotic. In some embodiments, the second therapeutic agent is viridicatumtoxin A, viridicatumtoxin B, vancomycin, tetracycline, spirohexaline, minocycline, tigecycline, doxycycline, a β -lactam antibiotic, an aminoglycoside antibiotic, 15 a sulfonamide antibiotic, a macrolide antibiotic, a glycopeptide antibiotic, an ansamycin antibiotic, an oxazolidinone antibiotic, a quinolone antibiotic, a streptogramin antibiotic, or a lipopeptide antibiotic.

In other embodiments, the microbial infection is a viral infection such as a poxvirus. In some embodiments, the poxvirus is variola virus, vaccinia virus, or *molluscum contagiosum*. In some embodiments, the methods further comprise administering a second therapeutic agent. In some embodiments, the second 20 therapeutic agent is an interferon or antiviral compound.

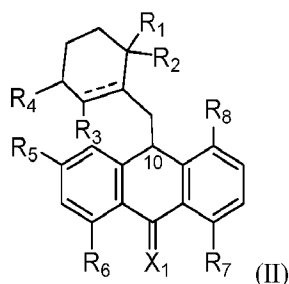
In other embodiments, the disease or disorder is cancer. In some embodiments, the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma. In some embodiments, the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, gastrointestinal tract, genitalia, genitourinary tract, head, kidney, larynx, 25 liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.

In some embodiments, the methods further comprise administering a second therapeutic agent. In some embodiments, the second therapeutic agent is a second chemotherapeutic agent, radiotherapy, immunotherapy, or surgery.

30 In still yet another aspect, the present disclosure provides methods of inhibiting the activity of a bacterial ribosome for the treatment of a disease or disorder comprising administering a compound or composition described herein.

In still yet another aspect, the present disclosure provides methods of inhibiting the activity of a bacterial UPP synthase for the treatment of a disease or disorder comprising administering a compound or 35 composition described herein.

In yet another aspect, the present disclosure provides methods of preparing a compound of the formula:



wherein:

R₁, R₂, and R₃ are each independently hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), cycloalkyl_(C≤8), or substituted cycloalkyl_(C≤8);

5 R₄ is hydroxy, alkylsilyloxy_(C≤18), substituted alkylsilyloxy_(C≤18), alkylarylsilyloxy_(C≤18), substituted alkylarylsilyloxy_(C≤18), alkylaralkylsilyloxy_(C≤18), substituted alkylaralkylsilyloxy_(C≤18), or –OR_a, wherein:

R_a is a hydroxy protecting group;

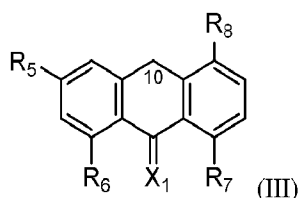
10 R₅, R₆, R₇, and R₈ are each independently hydroxy, alkoxy_(C≤12), substituted alkoxy_(C≤12), alkenyloxy_(C≤12), substituted alkenyloxy_(C≤12), alkynyloxy_(C≤12), substituted alkynyloxy_(C≤12), aryloxy_(C≤12), substituted aryloxy_(C≤12), aralkoxy_(C≤12), substituted aralkoxy_(C≤12), or –OR_b, wherein:

R_b is a hydroxy protecting group;

X₁ is O or NR_c, wherein:

15 R_c is hydrogen, alkyl_(C≤18), or substituted alkyl_(C≤8);

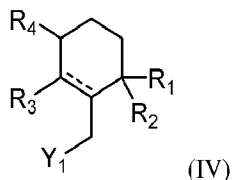
comprising reacting a compound of the formula:



wherein:

R₅, R₆, R₇, and R₈ are as defined above;

20 with a compound of the formula:

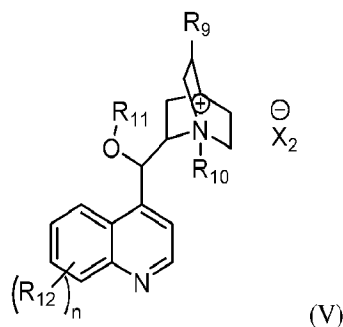


wherein:

R₅, R₆, R₇, and R₈ are as defined above;

Y₁ is a leaving group;

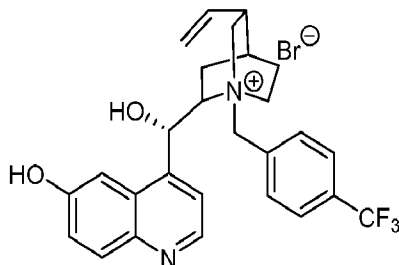
in the presence of a phase transfer catalyst and a base under conditions sufficient to cause a reaction. In some embodiments, the phase transfer catalyst is a compound of the formula:



wherein:

- 5 R₉ is alkyl_(C≤8), alkenyl_(C≤8), or a substituted version of either of these groups;
- R₁₀ and R₁₁ are each independently alkyl_(C≤18), alkenyl_(C≤18), aryl_(C≤18), aralkyl_(C≤18), or a substituted version of any of these groups;
- R₁₂ is hydrogen, hydroxy, alkoxy_(C≤12), substituted alkoxy_(C≤12), acyloxy_(C≤12), substituted acyloxy_(C≤12), aralkyl_(C≤12), or substituted aralkyl_(C≤12);
- 10 X₂ is a monovalent anion; and
- n is 1, 2, or 3.

In some embodiments, the phase transfer catalyst is a compound of the formula:

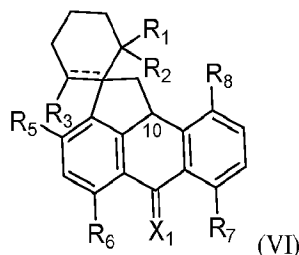


- In some embodiments, the base is a metal carbonate such as cesium carbonate. In some embodiments, the methods comprise adding the base as a solution in water. In some embodiments, the base as a solution in water comprises 20% to about 60% base. In some embodiments, the base as a solution in water comprises 40% base.

- In some embodiments, the methods comprise adding from about 5 equivalents to about 25 equivalents of the base relative to the compound of formula III. In some embodiments, the methods comprise adding about 10 equivalents of the base. In some embodiments, the methods comprise adding from about 1.0 equivalents to about 5 equivalents of the compound of formula IV relative to the compound of formula III. In some embodiments, the methods comprise adding about 1.1 equivalents of the compound of formula IV. In some embodiments, the methods comprise adding from about 0.1 mol% to about 20 mol% of the phase transfer catalyst. In some embodiments, the methods comprise adding from about 0.1 mol% to about 5 mol% of the phase transfer catalyst.

In some embodiments, the methods further comprise an organic solvent. In some embodiments, the organic solvent is a haloalkane_(C_≤8) such as dichloroethane or methylene chloride. In some embodiments, the methods further comprise reacting at a temperature from about -80 °C to about 25 °C such as from about -40 °C to about 0 °C. In some embodiments, the methods comprise reacting for a time period from about 6 hours
5 to about 1 week such as about 1 day to about 4 days.

In some embodiments, the methods further comprise reacting the compound of formula II with a fluoride source to produce a compound of formula:



wherein:

10 R₁, R₂, and R₃ are each independently hydrogen, alkyl_(C_≤8), substituted alkyl_(C_≤8), cycloalkyl_(C_≤8), or substituted cycloalkyl_(C_≤8);

R₅, R₆, R₇, and R₈ are each independently hydroxy, alkoxy_(C_≤12), substituted alkoxy_(C_≤12), alkenyloxy_(C_≤12), substituted alkenyloxy_(C_≤12), alkynyloxy_(C_≤12), substituted alkynyloxy_(C_≤12), aryloxy_(C_≤12), substituted aryloxy_(C_≤12), aralkoxy_(C_≤12), substituted aralkoxy_(C_≤12), or -OR_b,
15 wherein:

R_b is a hydroxy protecting group;

X₁ is O or NR_c, wherein:

R_c is hydrogen, alkyl_(C_≤18), or substituted alkyl_(C_≤8);

or a salt thereof. In some embodiments, the methods further comprise a purification step.

20 In some embodiments, one or more steps of the reaction further comprises purifying the reaction in a purification step. In some embodiments, the purification method is chromatography. In some embodiments, the purification method is column chromatography or high performance liquid chromatography.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein. For example, an aldehyde synthesized by one method
25 may be used in the preparation of a final compound according to a different method.

The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.” The word “about” means plus or minus 5% of the stated number.

Other objects, features and advantages of the present disclosure will become apparent from the
30 following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE FIGURES

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The disclosure may be better understood by reference to one or more of these drawings in combination with the detailed.

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FIGS. 1A & B – Structures of bacterial tetracyclines and designed analogs (**1A**) and fungal tetracyclines (**1B**)

FIG. 2 – The X-ray derived ORTEP representation of **6a**.

FIG. 3 – Molecular structures of viridicatumtoxins (**1** and **2**) and spirohexaline (**3**).

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FIG. 4 – The X-ray derived ORTEP representation of (–)-**11**.

FIG. 5 – Proposed mechanism of stereoselective spirocyclization of substituted anthrone (**6S,17R**)-**6** to pentacycle (**6S,15R**)-**4** through carbonium species **A** (viridicatumtoxin numbering for all intermediates and compounds).

FIG. 6 – The X-ray derived ORTEP representation of (+)-**11**.

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DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present disclosure relates to a series of analogs of viridicatumtoxin and an improved synthetic pathway to obtain viridicatumtoxin and its analogs. In some aspects, the analogs of the fungal secondary metabolites viridicatumtoxin A and B are useful as potent antibiotics against a variety of Gram-positive and certain Gram-negative bacterial strains. In the present disclosure, a collection of viridicatumtoxin analogs are synthesized and their antibiotic profile is evaluated. Additionally, this class of compounds has shown activity in a number of cancer cell lines. These and other aspects of the disclosure are described in greater detail below.

I. Compounds and Formulations Thereof

The compounds provided by the present disclosure are shown, for example, above in the summary section and in the claims below. They may be made using the methods outlined in the Examples section. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2007), which is incorporated by reference herein.

The viridicatumtoxin analogs of the present disclosure may contain one or more asymmetrically-substituted carbon or nitrogen atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a chemical formula are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Compounds may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In some embodiments, a single diastereomer is obtained. The chiral centers of the compounds of the present disclosure can have the (*S*) or the (*R*) configuration.

Chemical formulas used to represent the viridicatumtoxin analogs of the present disclosure will typically only show one of possibly several different tautomers. For example, many types of ketone groups are known to exist in equilibrium with corresponding enol groups. Similarly, many types of imine groups exist in equilibrium with enamine groups. Regardless of which tautomer is depicted for a given compound, and regardless of which one is most prevalent, all tautomers of a given chemical formula are intended.

The viridicatumtoxin analogs of the present disclosure may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the indications stated herein or otherwise.

In addition, atoms making up the viridicatumtoxin analogs of the present disclosure are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ¹³C and ¹⁴C.

The viridicatumtoxin analogs of the present disclosure may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, *etc.*), the compounds employed in some methods of the present disclosure may, if desired, be

delivered in prodrug form. Thus, the present disclosure contemplates prodrugs of compounds of the present disclosure as well as methods of delivering prodrugs. Prodrugs of the compounds employed in the disclosure may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a hydroxy, amino, or carboxylic acid, respectively.

It should be recognized that the particular anion or cation forming a part of any salt form of a compound provided herein is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002), which is incorporated herein by reference.

It will be appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates." Where the solvent is water, the complex is known as a "hydrate." It will also be appreciated that many organic compounds can exist in more than one solid form, including crystalline and amorphous forms. All solid forms of the compounds provided herein, including any solvates thereof are within the scope of the present disclosure.

B. Formulations

In some embodiments of the present disclosure, the compounds are included a pharmaceutical formulation. Materials for use in the preparation of microspheres and/or microcapsules are, *e.g.*, biodegradable/bioerodible polymers such as polygalactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutamine), and poly(lactic acid). Biocompatible carriers that may be used when formulating a controlled release parenteral formulation are carbohydrates (*e.g.*, dextrans), proteins (*e.g.*, albumin), lipoproteins, or antibodies. Materials for use in implants can be non-biodegradable (*e.g.*, polydimethyl siloxane) or biodegradable (*e.g.*, poly(caprolactone), poly(lactic acid), poly(glycolic acid) or poly(ortho esters) or combinations thereof).

Formulations for oral use include tablets containing the active ingredient(s) (*e.g.*, viridicatumtoxin and its derivatives) in a mixture with non-toxic pharmaceutically acceptable excipients. Such formulations are known to the skilled artisan. Excipients may be, for example, inert diluents or fillers (*e.g.*, sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (*e.g.*, cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (*e.g.*, sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (*e.g.*, magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

The tablets may be uncoated or they may be coated by known techniques, optionally to delay disintegration and absorption in the gastrointestinal tract and thereby providing a sustained action over a longer period. The coating may be adapted to release the active drug in a predetermined pattern (*e.g.*, in order to achieve a controlled release formulation) or it may be adapted not to release the active drug until after passage of the stomach (enteric coating). The coating may be a sugar coating, a film coating (*e.g.*, based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acrylate copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or an enteric coating (*e.g.*, based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, and/or ethylcellulose). Furthermore, a time delay material, such as, *e.g.*, glyceryl monostearate or glyceryl distearate may be employed.

II. Microbial Infections

A. Bacterial Infections

In some aspects of the present disclosure, the compounds disclosed herein may be used to treat a bacterial infection. While humans contain numerous different bacteria on and inside their bodies, an imbalance in bacterial levels or the introduction of pathogenic bacteria can cause a symptomatic bacterial infection. Pathogenic bacteria cause a variety of different diseases including but not limited to numerous foodborne illness, typhoid fever, tuberculosis, pneumonia, syphilis, and leprosy.

Additionally, different bacteria have a wide range of interactions with the body and those interactions can modulate ability of the bacteria to cause an infection. For example, bacteria can be conditionally pathogenic such that they only cause an infection under specific conditions. For example, *Staphylococcus* and *Streptococcus* bacteria exist in the normal human bacterial biome, but these bacteria when they are allowed to colonize other parts of the body causing a skin infection, pneumonia, or sepsis. Other bacteria are known as opportunistic pathogens and only cause diseases in a patient with a weakened immune system or another disease or disorder.

Bacteria can also be intracellular pathogens which can grow and reproduce within the cells of the host organism. Such bacteria can be divided into two major categories as either obligate intracellular parasites or facultative intracellular parasites. Obligate intracellular parasites require the host cell in order to reproduce and include such bacteria as but are not limited to *Chlamydomphila*, *Rickettsia*, and *Ehrlichia* which are known to cause pneumonia, urinary tract infections, typhus, and Rocky Mountain spotted fever. Facultative intracellular parasites can reproduce either intracellular or extracellular. Some non-limiting examples of facultative intracellular parasites include *Salmonella*, *Listeria*, *Legionella*, *Mycobacterium*, and *Brucella* which are known to cause food poisoning, typhoid fever, sepsis, meningitis, Legionnaire's disease, tuberculosis, leprosy, and brucellosis.

Finally, bacterial infections could be targeted to a specific location in or on the body. For example, bacteria could be harmless if only exposed to the specific organs, but when it comes in contact with a specific organ or tissue, the bacteria can begin replicating and cause a bacterial infection.

In particular, the inventors contemplate treatment of bacterial infections, including those caused by *Staphylococcus aureus*. *S. aureus* is a major human pathogen, causing a wide variety of illnesses ranging from

mild skin and soft tissue infections and food poisoning to life-threatening illnesses such as deep post-surgical infections, septicaemia, endocarditis, necrotizing pneumonia, and toxic shock syndrome. These organisms have a remarkable ability to accumulate additional antibiotic resistance determinants, resulting in the formation of multiply-drug-resistant strains.

5 Methicillin, being the first semi-synthetic penicillin to be developed, was introduced in 1959 to overcome the problem of penicillin-resistant *S. aureus* due to β -lactamase (penicillinase) production (Livermore, 2000). However, methicillin-resistant *S. aureus* (MRSA) strains were identified soon after the introduction of methicillin (Barber, 1961; Jevons, 1961). MRSA have acquired and integrated into their genome a 21- to 67-kb mobile genetic element, termed the staphylococcal cassette chromosome mec (SCCmec) that harbors the
10 methicillin resistance (*mecA*) gene and other antibiotic resistance determinants (Ito *et al.*, 2001; Ito *et al.*, 2004; Ma *et al.*, 2002). The *mecA* gene encodes an altered additional low affinity penicillin-binding protein (PBP2a) that confers broad resistance to all penicillin-related compounds including cephalosporins and carbapenems that are currently some of the most potent broad-spectrum drugs available (Hackbarth & Chambers, 1989). Since their first identification, strains of MRSA have spread and become established as major nosocomial (hospital-
15 acquired (HA)-MRSA) pathogens worldwide (Ayliffe, 1997; Crossley *et al.*, 1979; Panlilio *et al.*, 1992; Voss *et al.*, 1994). These organisms have evolved and emerged as a major cause of community-acquired infections (CA-MRSA) in healthy individuals lacking traditional risk factors for infection, and are causing community-outbreaks, which pose a significant threat to public health.

20 i. Gram-Positive Bacteria

In some aspects of the present disclosure, the compounds disclosed herein may be used to treat a bacterial infection by a Gram-positive bacteria. Gram-positive bacteria contain a thick peptidoglycan layer within the cell wall which prevents the bacteria from releasing the stain when dyed with crystal violet. Without being bound by theory, the Gram-positive bacteria are often more susceptible to antibiotics. Generally, Gram-
25 positive bacteria, in addition to the thick peptidoglycan layer, also comprise a lipid monolayer and contain teichoic acids which react with lipids to form lipoteichoic acids that can act as a chelating agent. Additionally, in Gram-positive bacteria, the peptidoglycan layer is outer surface of the bacteria. Many Gram-positive bacteria have been known to cause disease including, but are not limited to, *Streptococcus*, *Staphylococcus*, *Corynebacterium*, *Enterococcus*, *Listeria*, *Bacillus*, *Clostridium*, *Rathyabacter*, *Leifsonia*, and *Clavibacter*.

30 ii. Gram-Negative Bacteria

In some aspects of the present disclosure, the compounds disclosed herein may be used to treat a bacterial infection by a Gram-negative bacteria. Gram-negative bacteria do not retain the crystal violet stain after washing with alcohol. Gram-negative bacteria, on the other hand, have a thin peptidoglycan layer with an
35 outer membrane of lipopolysaccharides and phospholipids as well as a space between the peptidoglycan and the outer cell membrane called the periplasmic space. Gram-negative bacterial generally do not have teichoic acids or lipoteichoic acids in their outer coating. Generally, Gram-negative bacteria also release some endotoxin and contain prions which act as molecular transport units for specific compounds. Most bacteria are Gram-negative. Some non-limiting examples of Gram-negative bacteria include *Bordetella*, *Borrelia*, *Burcelia*,

Campylobacteria, Escherichia, Francisella, Haemophilus, Helicobacter, Legionella, Leptospira, Neisseria, Pseudomonas, Rickettsia, Salmonella, Shigella, Treponema, Vibrio, and Yersinia.

iii. Gram-Indeterminate Bacteria

In some aspects of the present disclosure, the compounds disclosed herein may be used to treat a bacterial infection by a Gram-indeterminate bacteria. Gram-indeterminate bacteria do not full stain or partially stain when exposed to crystal violet. Without being bound by theory, a Gram-indeterminate bacteria may exhibit some of the properties of the Gram-positive and Gram-negative bacteria. A non-limiting example of a Gram-indeterminate bacteria include *Mycobacterium tuberculosis* or *Mycobacterium leprae*.

B. Viral Infections

In some aspects of the present disclosure, the compounds disclosed herein may be used to treat a viral infection. Similarly, virus can also exist in pathogenic form which can lead to human diseases. Viral infections are typically not treated directly but rather symptomatically since virus often have a self-limiting life cycle. Viral infections can also be more difficult to diagnosis than a bacterial infection since viral infections often do result in the concomitant increase in white blood cell counts. Some non-limiting examples of pathogenic virus include influenza virus, smallpox, BK virus, JC virus, human papillomavirus, adenovirus, herpes simplex type 1, herpes simplex type 2, varicella-zoster virus, Epstein barr virus, human cytomegalovirus, human herpesvirus type 8, Norwalk virus, human bocavirus, rubella virus, hepatitis E virus, hepatitis B virus, human immunodeficiency virus (HIV), Ebola virus, rabies virus, rotavirus, and hepatitis D virus.

III. Hyperproliferative Diseases

A. Cancer and Other Hyperproliferative Disease

While hyperproliferative diseases can be associated with any disease which causes a cell to begin to reproduce uncontrollably, the prototypical example is cancer. One of the key elements of cancer is that the cell's normal apoptotic cycle is interrupted and thus agents that interrupt the growth of the cells are important as therapeutic agents for treating these diseases. In this disclosure, the viridicatumtoxin derivatives may be used to lead to decreased cell counts and as such can potentially be used to treat a variety of types of cancer lines. In various aspects, it is anticipated that the viridicatumtoxin derivatives of the present disclosure may be used to treat virtually any malignancy.

Cancer cells that may be treated with the compounds of the present disclosure include but are not limited to cells from the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, pancreas, testis, tongue, cervix, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; branchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma;

acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometroid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma;

5 cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; androblastoma, malignant;

10 sertoli cell carcinoma; leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malig melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar

15 rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma;

20 osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar

25 sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; hodgkin's disease; hodgkin's; paraganuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative

30 small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia. In certain aspects, the tumor may comprise an osteosarcoma, angiosarcoma, rhabdosarcoma, leiomyosarcoma, Ewing sarcoma, glioblastoma, neuroblastoma, or leukemia.

35 III. Therapies

A. Pharmaceutical Formulations and Routes of Administration

Where clinical applications are contemplated, it will be necessary to prepare pharmaceutical compositions in a form appropriate for the intended application. In some embodiments, such formulation with

the compounds of the present disclosure is contemplated. Generally, this will entail preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

One will generally desire to employ appropriate salts and buffers to render delivery vectors stable and allow for uptake by target cells. Buffers also will be employed when recombinant cells are introduced into a patient. Aqueous compositions of the present disclosure comprise an effective amount of the vector to cells, dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. Such compositions also are referred to as inocula. The phrase "pharmaceutically or pharmacologically acceptable" refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the vectors or cells of the present disclosure, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

The active compositions of the present disclosure may include classic pharmaceutical preparations. Administration of these compositions according to the present disclosure will be via any common route so long as the target tissue is available via that route. Such routes include oral, nasal, buccal, rectal, vaginal or topical route. Alternatively, administration may be by orthotopic, intradermal, subcutaneous, intramuscular, intratumoral, intraperitoneal, or intravenous injection. Such compositions would normally be administered as pharmaceutically acceptable compositions, described *supra*.

The active compounds may also be administered parenterally or intraperitoneally. Solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

For oral administration viridicatumtoxin and its derivatives may be incorporated with excipients and used in the form of non-ingestible mouthwashes and dentifrices. A mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an antiseptic wash containing sodium borate, glycerin and potassium bicarbonate. The active ingredient may also be dispersed in dentifrices, including: gels, pastes, powders and slurries. The active ingredient may be added in a therapeutically effective amount to a paste dentifrice that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants.

The compositions of the present disclosure may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include the acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug release capsules and the like. For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 mL of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences," 15th Edition, pages 1035–1038 and 1570–1580, 1990). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as

required by FDA's Division of Biological Standards and Quality Control of the Office of Compliance and Biologics Quality.

B. Methods of Treatment

In particular, the compositions that may be used in treating microbial infections and cancer in a subject (e.g., a human subject) are disclosed herein. The compositions described above are preferably administered to a mammal (e.g., rodent, human, non-human primates, canine, bovine, ovine, equine, feline, etc.) in an effective amount, that is, an amount capable of producing a desirable result in a treated subject (e.g., causing apoptosis of cancerous cells or killing bacterial cells). Toxicity and therapeutic efficacy of the compositions utilized in methods of the disclosure can be determined by standard pharmaceutical procedures. As is well known in the medical and veterinary arts, dosage for any one animal depends on many factors, including the subject's size, body surface area, body weight, age, the particular composition to be administered, time and route of administration, general health, the clinical symptoms of the infection or cancer and other drugs being administered concurrently. A composition as described herein is typically administered at a dosage that inhibits the growth or proliferation of a bacterial cell, inhibits the growth of a biofilm, or induces death of cancerous cells (e.g., induces apoptosis of a cancer cell), as assayed by identifying a reduction in hematological parameters (Complete blood count (CBC)), or cancer cell growth or proliferation. In some embodiments, in the experiments described herein and based upon dosing of other tetracycline compounds, the amount of the viridicatumtoxin derivatives used to inhibit bacterial growth, treat a viral infection, or induce apoptosis of the cancer cells is calculated to be from about 0.01 mg to about 10,000 mg/day. In some embodiments, the amount is from about 1 mg to about 1,000 mg/day. In some embodiments, these dosings may be reduced or increased based upon the biological factors of a particular patient such as increased or decreased metabolic breakdown of the drug or decreased uptake by the digestive tract if administered orally. Additionally, the new derivatives of viridicatumtoxin may be more efficacious and thus a smaller dose is required to achieve a similar effect. Such a dose is typically administered once a day for a few weeks or until sufficient reducing in cancer cells has been achieved.

The therapeutic methods of the disclosure (which include prophylactic treatment) in general include administration of a therapeutically effective amount of the compositions described herein to a subject in need thereof, including a mammal, particularly a human. Such treatment will be suitably administered to subjects, particularly humans, suffering from, having, susceptible to, or at risk for a disease, disorder, or symptom thereof. Determination of those subjects "at risk" can be made by any objective or subjective determination by a diagnostic test or opinion of a subject or health care provider (e.g., genetic test, enzyme or protein marker, marker (as defined herein), family history, and the like).

In one embodiment, the disclosure provides a method of monitoring treatment progress. The method includes the step of determining a level of changes in hematological parameters and/or cancer stem cell (CSC) analysis with cell surface proteins as diagnostic markers (which can include, for example, but are not limited to CD34, CD38, CD90, and CD117) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof associated with cancer (e.g., leukemia) in which the subject has been administered a therapeutic amount of a composition as described herein. The level of marker determined in the method can be compared to known levels of marker either in healthy normal controls or in other afflicted

patients to establish the subject's disease status. In preferred embodiments, a second level of marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of marker in the subject is determined prior to beginning treatment according to the methods described herein; this pre-treatment level of marker can then be compared to the level of marker in the subject after the treatment commences, to determine the efficacy of the treatment.

C. Combination Therapies

It is envisioned that the viridicatumtoxin derivatives described herein may be used in combination therapies with an additional antimicrobial agent such as anti-viral, antibiotic, or a compound which mitigates one or more of the side effects experienced by the patient.

Furthermore, it is very common in the field of cancer therapy to combine therapeutic modalities. The following is a general discussion of therapies that may be used in conjunction with the therapies of the present disclosure.

To treat cancers using the methods and compositions of the present disclosure, one would generally contact a tumor cell or subject with a compound and at least one other therapy. These therapies would be provided in a combined amount effective to achieve a reduction in one or more disease parameter(s). This process may involve contacting the cells/subjects with the both agents/therapies at the same time, *e.g.*, using a single composition or pharmacological formulation that includes both agents, or by contacting the cell/subject with two distinct compositions or formulations, at the same time, wherein one composition includes the compound and the other includes the other agent.

Alternatively, viridicatumtoxin derivatives of the present disclosure may precede or follow the other treatment by intervals ranging from minutes to weeks. One would generally ensure that a significant period of time did not expire between the time of each delivery, such that the therapies would still be able to exert an advantageously combined effect on the cell/subject. In such instances, it is contemplated that one would contact the cell with both modalities within about 12–24 hours of each other, within about 6–12 hours of each other, or with a delay time of only about 12 hours. In some situations, it may be desirable to extend the time period for treatment significantly; however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

It also is conceivable that more than one administration of either the compound or the other therapy will be desired. Various combinations may be employed, where a compound of the present disclosure is “A,” and the other therapy is “B,” as exemplified below:

A/B/A B/A/B B/B/A A/A/B B/A/A A/B/B B/B/B/A B/B/A/B
 A/A/B/B A/B/A/B A/B/B/A B/B/A/A B/A/B/A B/A/A/B B/B/B/A
 A/A/A/B B/A/A/A A/B/A/A A/A/B/A A/B/B/B B/A/B/B B/B/A/B

Antimicrobial agents or factors suitable for use in a combined therapy with agents according to the present disclosure against an infectious disease include antibiotics such as penicillins, cephalosporins, carbapenems, macrolides, aminoglycosides, quinolones (including fluoroquinolones), sulfonamides and

tetracyclines. In particular, one may use combination therapies for treating MRSA. Both CA-MRSA and HA-MRSA are resistant to traditional anti-staphylococcal beta-lactam antibiotics, such as cephalixin. CA-MRSA has a greater spectrum of antimicrobial susceptibility, including to sulfa drugs (like co-trimoxazole/trimethoprim-sulfamethoxazole), tetracyclines (like doxycycline and minocycline) and clindamycin (for osteomyelitis), but the drug of choice for treating CA-MRSA is now believed to be vancomycin, according to a Henry Ford Hospital Study. HA-MRSA is resistant even to these antibiotics and often is susceptible only to vancomycin. Newer drugs, such as linezolid (belonging to the newer oxazolidinones class) and daptomycin, are effective against both CA-MRSA and HA-MRSA. The Infectious Disease Society of America recommends vancomycin, linezolid, or clindamycin (if susceptible) for treating patients with MRSA pneumonia. Ceftaroline, a fifth generation cephalosporin, is the first beta-lactam antibiotic approved in the U.S. to treat MRSA infections (skin and soft tissue or community acquired pneumonia only).

Quinolone-resistant *S. aureus* is another emerging pathogen that may be treated with compounds according to the present disclosure, optionally in combination with vancomycin, teicoplanin and linezolid.

Vancomycin and teicoplanin are glycopeptide antibiotics used to treat MRSA infections. Teicoplanin is a structural congener of vancomycin that has a similar activity spectrum but a longer half-life. Because the oral absorption of vancomycin and teicoplanin is very low, these agents must be administered intravenously to control systemic infections. Treatment of MRSA infection with vancomycin can be complicated, due to its inconvenient route of administration. Moreover, many clinicians believe that the efficacy of vancomycin against MRSA is inferior to that of anti-staphylococcal beta-lactam antibiotics against methicillin-susceptible *Staphylococcus aureus* (MSSA).

Several newly discovered strains of MRSA show antibiotic resistance even to vancomycin and teicoplanin. These new evolutions of the MRSA bacterium have been dubbed Vancomycin intermediate-resistant *Staphylococcus aureus* (VISA). Linezolid, quinupristin/dalfopristin, daptomycin, ceftaroline, and tigecycline are used to treat more severe infections that do not respond to glycopeptides such as vancomycin. Current guidelines recommend daptomycin for VISA bloodstream infections and endocarditis. Studies also suggest that allicin, a compound found in garlic, may prove to be effective in the treatment of MRSA.

Other combinations are contemplated. The following is a general discussion of antibiotic, antiviral, and cancer therapies that may be used in combination with the compounds of the present disclosure.

1. Antibiotics

The term "antibiotics" are drugs which may be used to treat a bacterial infection through either inhibiting the growth of bacteria or killing bacteria. Without being bound by theory, it is believed that antibiotics can be classified into two major classes: bactericidal agents that kill bacteria or bacteriostatic agents that slow down or prevent the growth of bacteria.

The first commercially available antibiotic was released in the 1930's. Since then, many different antibiotics have been developed and widely prescribed. In 2010, on average, 4 in 5 Americans are prescribed antibiotics annually. Given the prevalence of antibiotics, bacteria have started to develop resistance to specific

antibiotics and antibiotic mechanisms. Without being bound by theory, the use of antibiotics in combination with another antibiotic may modulate resistance and enhance the efficacy of one or both agents.

In some embodiments, antibiotics can fall into a wide range of classes. In some embodiments, the compounds of the present disclosure may be used in conjunction with another antibiotic. In some embodiments, the compounds may be used in conjunction with a narrow spectrum antibiotic which targets a specific bacteria type. In some non-limiting examples of bactericidal antibiotics include penicillin, cephalosporin, polymyxin, rifamycin, lipiarmycin, quinolones, and sulfonamides. In some non-limiting examples of bacteriostatic antibiotics include macrolides, lincosamides, or tetracyclines. In some embodiments, the antibiotic is an aminoglycoside such as kanamycin and streptomycin, an ansamycin such as rifaximin and geldanamycin, a carbacephem such as loracarbef, a carbapenem such as ertapenem, imipenem, a cephalosporin such as cephalexin, cefixime, cefepime, and ceftobiprole, a glycopeptide such as vancomycin or teicoplanin, a lincosamide such as lincomycin and clindamycin, a lipopeptide such as daptomycin, a macrolide such as clarithromycin, spiramycin, azithromycin, and telithromycin, a monobactam such as aztreonam, a nitrofurantoin such as furazolidone and nitrofurantoin, an oxazolidinone such as linezolid, a penicillin such as amoxicillin, azlocillin, flucloxacillin, and penicillin G, an antibiotic polypeptide such as bacitracin, polymyxin B, and colistin, a quinolone such as ciprofloxacin, levofloxacin, and gatifloxacin, a sulfonamide such as silver sulfadiazine, mefenide, sulfadimethoxine, or sulfasalazine, or a tetracycline such as demeclocycline, doxycycline, minocycline, oxytetracycline, or tetracycline. In some embodiments, the compounds could be combined with a drug which acts against mycobacteria such as cycloserine, capreomycin, ethionamide, rifampicin, rifabutin, rifapentine, and streptomycin. Other antibiotics that are contemplated for combination therapies may include arspenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin, dalfopristin, thiamphenicol, tigecycline, tinidazole, or trimethoprim.

2. Antivirals

The term “antiviral” or “antiviral agents” are drugs which may be used to treat a viral infection. In general, antiviral agents act via two major mechanisms: preventing viral entry into the cell and inhibiting viral synthesis. Without being bound by theory, viral replication can be inhibited by using agents that mimic either the virus-associated proteins and thus block the cellular receptors or using agents that mimic the cellular receptors and thus block the virus-associated proteins. Furthermore, agents which cause an uncoating of the virus can also be used as antiviral agents.

The second mechanism of viral inhibition is preventing or interrupting viral synthesis. Such drugs can target different proteins associated with the replication of viral DNA including reverse transcriptase, integrase, transcription factors, or ribozymes. Additionally, the therapeutic agent interrupts translation by acting as an antisense DNA strain, inhibiting the formation of protein processing or assembly, or acting as virus protease inhibitors. Finally, an anti-viral agent could additionally inhibit the release of the virus after viral production in the cell.

Additionally, anti-viral agents could modulate the body's own immune system to fight a viral infection. Without being bound by theory, the anti-viral agent which stimulates the immune system may be used with a wide variety of viral infections.

In some embodiments, the present disclosure provides methods of using the disclosed compounds in a combination therapy with an anti-viral agent as described above. In some non-limiting examples, the anti-viral agent is abacavir, aciclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atipla, balavir, boceprevir, tetra, cidofovir, combivir, dolutegravir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, ecoliever, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type I, type II, and type III, lamivudine, lopinavir, lovirode, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, pyrimidine, saquinavir, sofosbuvir, stavudine, telaprevir, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, traproved, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, or zidovudine. In some embodiments, the anti-viral agents is an anti-retroviral, a fusion inhibitor, an integrase inhibitor, an interferon, a nucleoside analogues, a protease inhibitor, a reverse transcriptase inhibitor, a synergistic enhancer, or a natural product such as tea tree oil.

3. Chemotherapy

The term “chemotherapy” refers to the use of drugs to treat cancer. A “chemotherapeutic agent” is used to connote a compound or composition that is administered in the treatment of cancer. These agents or drugs are categorized by their mode of activity within a cell, for example, whether and at what stage they affect the cell cycle. Alternatively, an agent may be characterized based on its ability to directly cross-link DNA, to intercalate into DNA, or to induce chromosomal and mitotic aberrations by affecting nucleic acid synthesis. Most chemotherapeutic agents fall into the following categories: alkylating agents, antimetabolites, antitumor antibiotics, mitotic inhibitors, and nitrosoureas.

Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin γ_1^I and calicheamicin ω_1^I ; dynemicin, including dynemicin A uncilamycin and derivatives thereof; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabacin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin,

esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanane, testolactone; anti-adrenals such as aminogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.*, paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (*e.g.*, CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; cisplatin (CDDP), carboplatin, procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, busulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, raloxifene, estrogen receptor binding agents, taxol, paclitaxel, docetaxel, gemcitabien, navelbine, farnesyl-protein transferase inhibitors, transplatinum, 5-fluorouracil, vincristin, vinblastin and methotrexate and pharmaceutically acceptable salts, acids or derivatives of any of the above.

4. Radiotherapy

Radiotherapy, also called radiation therapy, is the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow. Although radiation damages both cancer cells and normal cells, the latter are able to repair themselves and function properly.

Radiation therapy used according to the present disclosure may include, but is not limited to, the use of γ -rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated such as microwaves and UV-irradiation. It is most likely that all of these factors induce a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 12.9 to 51.6 mC/kg for prolonged periods of time (3 to 4 wk), to single doses of 0.516 to 1.55 C/kg. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

Radiotherapy may comprise the use of radiolabeled antibodies to deliver doses of radiation directly to the cancer site (radioimmunotherapy). Antibodies are highly specific proteins that are made by the body in response to the presence of antigens (substances recognized as foreign by the immune system). Some tumor cells contain specific antigens that trigger the production of tumor-specific antibodies. Large quantities of these antibodies can be made in the laboratory and attached to radioactive substances (a process known as radiolabeling). Once injected into the body, the antibodies actively seek out the cancer cells, which are destroyed by the cell-killing (cytotoxic) action of the radiation. This approach can minimize the risk of radiation damage to normal cells.

Conformal radiotherapy uses the same radiotherapy machine, a linear accelerator, as the normal radiotherapy treatment but metal blocks are placed in the path of the x-ray beam to alter its shape to match that of the cancer. This ensures that a higher radiation dose is given to the tumor. Normal surrounding cells and nearby structures receive a lower dose of radiation, so the possibility of side effects is reduced. A device called a multi-leaf collimator has been developed and may be used as an alternative to the metal blocks. The multi-leaf collimator consists of a number of metal sheets which are fixed to the linear accelerator. Each layer can be adjusted so that the radiotherapy beams can be shaped to the treatment area without the need for metal blocks. Precise positioning of the radiotherapy machine is very important for conformal radiotherapy treatment and a special scanning machine may be used to check the position of internal organs at the beginning of each treatment.

High-resolution intensity modulated radiotherapy also uses a multi-leaf collimator. During this treatment the layers of the multi-leaf collimator are moved while the treatment is being given. This method is likely to achieve even more precise shaping of the treatment beams and allows the dose of radiotherapy to be constant over the whole treatment area.

Although research studies have shown that conformal radiotherapy and intensity modulated radiotherapy may reduce the side effects of radiotherapy treatment, it is possible that shaping the treatment area so precisely could stop microscopic cancer cells just outside the treatment area being destroyed. This means that the risk of the cancer coming back in the future may be higher with these specialized radiotherapy techniques.

Scientists also are looking for ways to increase the effectiveness of radiation therapy. Two types of investigational drugs are being studied for their effect on cells undergoing radiation. Radiosensitizers make the tumor cells more likely to be damaged, and radioprotectors protect normal tissues from the effects of radiation. Hyperthermia, the use of heat, is also being studied for its effectiveness in sensitizing tissue to radiation.

5. Immunotherapy

In the context of cancer treatment, immunotherapeutics, generally, rely on the use of immune effector cells and molecules to target and destroy cancer cells. Trastuzumab (Herceptin™) is such an example. The immune effector may be, for example, an antibody specific for some marker on the surface of a tumor cell. The antibody alone may serve as an effector of therapy or it may recruit other cells to actually affect cell killing. The antibody also may be conjugated to a drug or toxin (chemotherapeutic, radionuclide, ricin A chain, cholera toxin, pertussis toxin, *etc.*) and serve merely as a targeting agent. Alternatively, the effector may be a lymphocyte carrying a surface molecule that interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells and NK cells. The combination of therapeutic modalities, *i.e.*,

direct cytotoxic activity and inhibition or reduction of ErbB2 would provide therapeutic benefit in the treatment of ErbB2 overexpressing cancers.

In one aspect of immunotherapy, the tumor cell must bear some marker that is amenable to targeting, *i.e.*, is not present on the majority of other cells. Many tumor markers exist and any of these may be suitable for targeting in the context of the present disclosure. Common tumor markers include carcinoembryonic antigen, prostate specific antigen, urinary tumor associated antigen, fetal antigen, tyrosinase (p97), gp68, TAG-72, HMFG, Sialyl Lewis Antigen, MucA, MucB, PLAP, estrogen receptor, laminin receptor, erb B and p155. An alternative aspect of immunotherapy is to combine anticancer effects with immune stimulatory effects. Immune stimulating molecules also exist including: cytokines such as IL-2, IL-4, IL-12, GM-CSF, γ -IFN, chemokines such as MIP-1, MCP-1, IL-8 and growth factors such as FLT3 ligand. Combining immune stimulating molecules, either as proteins or using gene delivery in combination with a tumor suppressor has been shown to enhance anti-tumor effects (Ju *et al.*, 2000). Moreover, antibodies against any of these compounds may be used to target the anti-cancer agents discussed herein.

Examples of immunotherapies currently under investigation or in use are immune adjuvants *e.g.*, *Mycobacterium bovis*, *Plasmodium falciparum*, dinitrochlorobenzene and aromatic compounds (U.S. Patents 5,801,005 and 5,739,169; Hui and Hashimoto, 1998; Christodoulides *et al.*, 1998), cytokine therapy, *e.g.*, interferons α , β , and γ ; IL-1, GM-CSF and TNF (Bukowski *et al.*, 1998; Davidson *et al.*, 1998; Hellstrand *et al.*, 1998) gene therapy, *e.g.*, TNF, IL-1, IL-2, p53 (Qin *et al.*, 1998; Austin-Ward and Villasaca, 1998; U.S. Patents 5,830,880 and 5,846,945) and monoclonal antibodies, *e.g.*, anti-ganglioside GM2, anti-HER-2, anti-p185 (Pietras *et al.*, 1998; Hanibuchi *et al.*, 1998; U.S. Patent 5,824,311). It is contemplated that one or more anti-cancer therapies may be employed with the gene silencing therapies described herein.

In active immunotherapy, an antigenic peptide, polypeptide or protein, or an autologous or allogenic tumor cell composition or "vaccine" is administered, generally with a distinct bacterial adjuvant (Ravindranath and Morton, 1991; Morton *et al.*, 1992; Mitchell *et al.*, 1990; Mitchell *et al.*, 1993).

In adoptive immunotherapy, the patient's circulating lymphocytes, or tumor-infiltrated lymphocytes, are isolated *in vitro*, activated by lymphokines such as IL-2 or transduced with genes for tumor necrosis, and readministered (Rosenberg *et al.*, 1988; 1989).

6. Surgery

Approximately 60% of persons with cancer will undergo surgery of some type, which includes preventative, diagnostic or staging, curative, and palliative surgery. Curative surgery is a cancer treatment that may be used in conjunction with other therapies, such as the treatment of the present disclosure, chemotherapy, radiotherapy, hormonal therapy, gene therapy, immunotherapy and/or alternative therapies.

Curative surgery includes resection in which all or part of cancerous tissue is physically removed, excised, and/or destroyed. Tumor resection refers to physical removal of at least part of a tumor. In addition to tumor resection, treatment by surgery includes laser surgery, cryosurgery, electrosurgery, and microscopically controlled surgery (Mohs' surgery). It is further contemplated that the present disclosure may be used in conjunction with removal of superficial cancers, precancers, or incidental amounts of normal tissue.

Upon excision of part or all of cancerous cells, tissue, or tumor, a cavity may be formed in the body. Treatment may be accomplished by perfusion, direct injection or local application of the area with an additional anti-cancer therapy. Such treatment may be repeated, for example, every 1, 2, 3, 4, 5, 6, or 7 days, or every 1, 2, 3, 4, and 5 weeks or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. These treatments may be of varying dosages as well.

In some particular embodiments, after removal of the tumor, an adjuvant treatment with a compound of the present disclosure is believed to be particularly efficacious in reducing the reoccurrence of the tumor. Additionally, the compounds of the present disclosure can also be used in a neoadjuvant setting.

7. Other Agents

It is contemplated that other agents may be used with the present disclosure. These additional agents include immunomodulatory agents, agents that affect the upregulation of cell surface receptors and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion, agents that increase the sensitivity of the hyperproliferative cells to apoptotic inducers, or other biological agents. Immunomodulatory agents include tumor necrosis factor; interferon alpha, beta, and gamma; IL-2 and other cytokines; F42K and other cytokine analogs; or MIP-1, MIP-1 β , MCP-1, RANTES, and other chemokines. It is further contemplated that the upregulation of cell surface receptors or their ligands such as Fas/Fas ligand, DR4 or DR5/TRAIL (Apo-2 ligand) would potentiate the apoptotic inducing abilities of the present disclosure by establishment of an autocrine or paracrine effect on hyperproliferative cells. Increases in intercellular signaling by elevating the number of GAP junctions would increase the anti-hyperproliferative effects on the neighboring hyperproliferative cell population. In other embodiments, cytostatic or differentiation agents may be used in combination with the present disclosure to improve the anti-hyperproliferative efficacy of the treatments. Inhibitors of cell adhesion are contemplated to improve the efficacy of the present disclosure. Examples of cell adhesion inhibitors are focal adhesion kinase (FAKs) inhibitors and Lovastatin. It is further contemplated that other agents that increase the sensitivity of a hyperproliferative cell to apoptosis, such as the antibody c225, could be used in combination with the present disclosure to improve the treatment efficacy.

There have been many advances in the therapy of cancer following the introduction of cytotoxic chemotherapeutic drugs. However, one of the consequences of chemotherapy is the development/acquisition of drug-resistant phenotypes and the development of multiple drug resistance. The development of drug resistance remains a major obstacle in the treatment of such tumors and therefore, there is an obvious need for alternative approaches such as gene therapy.

Another form of therapy for use in conjunction with chemotherapy, radiation therapy or biological therapy includes hyperthermia, which is a procedure in which a patient's tissue is exposed to high temperatures (up to 106°F). External or internal heating devices may be involved in the application of local, regional, or whole-body hyperthermia. Local hyperthermia involves the application of heat to a small area, such as a tumor. Heat may be generated externally with high-frequency waves targeting a tumor from a device outside the body. Internal heat may involve a sterile probe, including thin, heated wires or hollow tubes filled with warm water, implanted microwave antennae, or radiofrequency electrodes.

A patient's organ or a limb is heated for regional therapy, which is accomplished using devices that produce high energy, such as magnets. Alternatively, some of the patient's blood may be removed and heated before being perfused into an area that will be internally heated. Whole-body heating may also be implemented in cases where cancer has spread throughout the body. Warm-water blankets, hot wax, inductive coils, and thermal chambers may be used for this purpose.

The skilled artisan is directed to "Remington's Pharmaceutical Sciences" 15th Edition, chapter 33, in particular pages 624-652. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

It also should be pointed out that any of the foregoing therapies may prove useful by themselves in treating cancer.

IV. Synthetic Methods

In some aspects, the compounds of this disclosure can be synthesized using the methods of organic chemistry as described in this application. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2007), which is incorporated by reference herein

A. Process Scale-Up

The synthetic methods described herein can be further modified and optimized for preparative, pilot- or large-scale production, either batch or continuous, using the principles and techniques of process chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *Practical Process Research & Development* (2000), which is incorporated by reference herein. The synthetic method described herein may be used to produce preparative scale amounts of viridicatumtoxin and derivatives thereof.

B. Chemical Definitions

When used in the context of a chemical group: "hydrogen" means -H; "hydroxy" means -OH; "oxo" means =O; "carbonyl" means -C(=O)-; "carboxy" means -C(=O)OH (also written as -COOH or -CO₂H); "halo" means independently -F, -Cl, -Br or -I; "amino" means -NH₂; "hydroxyamino" means -NHOH; "nitro" means -NO₂; imino means =NH; "cyano" means -CN; "isocyanate" means -N=C=O; "azido" means -N₃; in a monovalent context "phosphate" means -OP(O)(OH)₂ or a deprotonated form thereof; in a divalent context "phosphate" means -OP(O)(OH)O- or a deprotonated form thereof; "mercapto" means -SH; and "thio" means =S; "sulfo" means -SO₃H, "sulfonyl" means -S(O)₂-; and "sulfinyl" means -S(O)-.

In the context of chemical formulas, the symbol "-" means a single bond, "=" means a double bond, and "≡" means triple bond. The symbol "----" represents an optional bond, which if present is either single or

double. The symbol "====" represents a single bond or a double bond. Thus, for example, the formula

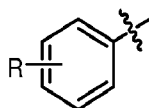


includes , , ,  and . And it is understood that no one such ring atom forms

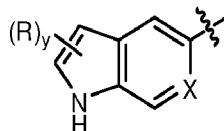
part of more than one double bond. Furthermore, it is noted that the covalent bond symbol “—”, when connecting one or two stereogenic atoms, does not indicate any preferred stereochemistry. Instead, it covers all stereoisomers as well as mixtures thereof. The symbol “”, when drawn perpendicularly across a bond

5 (e.g., —CH₃ for methyl) indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in unambiguously identifying a point of attachment. The symbol “” means a single bond where the group attached to the thick end of the wedge is “out of the page.” The symbol “” means a single bond where the group attached to the thick end of the wedge is “into the page”. The symbol “” means a single bond where the geometry around a double bond (e.g., either *E* or *Z*) is undefined. Both options, as well as combinations thereof are therefore intended. Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to that atom. A bold dot on a carbon atom indicates that the hydrogen attached to that carbon is oriented out of the plane of the paper.

When a group “R” is depicted as a “floating group” on a ring system, for example, in the formula:



15 then R may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed. When a group “R” is depicted as a “floating group” on a fused ring system, as for example in the formula:



20 then R may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (e.g., the hydrogen attached to the nitrogen in the formula above), implied hydrogens (e.g., a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (e.g., a hydrogen attached to group X, when X equals —CH—), so long as a stable structure is formed.

25 In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter “y” immediately following the group “R” enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

30 For the groups and classes below, the following parenthetical subscripts further define the group/class as follows: “(C_n)” defines the exact number (n) of carbon atoms in the group/class. “(C_{≤n})” defines the maximum number (n) of carbon atoms that can be in the group/class, with the minimum number as small as possible for the group in question, e.g., it is understood that the minimum number of carbon atoms in the group

“alkenyl_(C≤8)” or the class “alkene_(C≤8)” is two. For example, “alkoxy_(C≤10)” designates those alkoxy groups having from 1 to 10 carbon atoms. (Cn-n') defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Similarly, “alkyl_(C2-10)” designates those alkyl groups having from 2 to 10 carbon atoms.

The term “saturated” as used herein means the compound or group so modified has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. In the case of substituted versions of saturated groups, one or more carbon oxygen double bond or a carbon nitrogen double bond may be present. And when such a bond is present, then carbon-carbon double bonds that may occur as part of keto-enol tautomerism or imine/enamine tautomerism are not precluded.

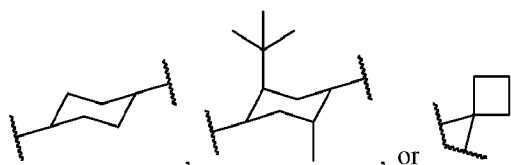
The term “aliphatic” when used without the “substituted” modifier signifies that the compound/group so modified is an acyclic or cyclic, but non-aromatic hydrocarbon compound or group. In aliphatic compounds/groups, the carbon atoms can be joined together in straight chains, branched chains, or non-aromatic rings (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single bonds (alkanes/alkyl), or unsaturated, with one or more double bonds (alkenes/alkenyl) or with one or more triple bonds (alkynes/alkynyl).

The term “alkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched acyclic structure, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_3$ (Me), $-\text{CH}_2\text{CH}_3$ (Et), $-\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Pr or propyl), $-\text{CH}(\text{CH}_3)_2$ (*i*-Pr, *Pr* or isopropyl), $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Bu), $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (*sec*-butyl), $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ (isobutyl), $-\text{C}(\text{CH}_3)_3$ (*tert*-butyl, *t*-butyl, *t*-Bu or *t*Bu), and $-\text{CH}_2\text{C}(\text{CH}_3)_3$ (*neo*-pentyl) are non-limiting examples of alkyl groups. The term “alkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, $-\text{CH}_2-$ (methylene), $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2-$ are non-limiting examples of alkanediyl groups. The term “alkylidene” when used without the “substituted” modifier refers to the divalent group $=\text{CRR}'$ in which R and R' are independently hydrogen or alkyl. Non-limiting examples of alkylidene groups include: $=\text{CH}_2$, $=\text{CH}(\text{CH}_2\text{CH}_3)$, and $=\text{C}(\text{CH}_3)_2$. An “alkane” refers to the compound H-R, wherein R is alkyl as this term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The following groups are non-limiting examples of substituted alkyl groups: $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CH}_2\text{Cl}$. The term “haloalkyl” is a subset of substituted alkyl, in which one or more hydrogen atoms has been substituted with a halo group and no other atoms aside from carbon, hydrogen and halogen are present. The group, $-\text{CH}_2\text{Cl}$ is a non-limiting example of a haloalkyl. The term “fluoroalkyl” is a subset of substituted alkyl, in which one or more hydrogen has been substituted with a fluoro group and no other atoms aside from carbon, hydrogen and fluorine are present. The groups, $-\text{CH}_2\text{F}$, $-\text{CF}_3$, and $-\text{CH}_2\text{CF}_3$ are non-limiting examples of fluoroalkyl groups.

The term “cycloalkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, said carbon atom forms part of one or more non-

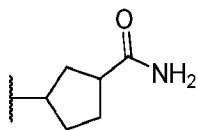
aromatic ring structures, a cyclo or cyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of cycloalkyl groups include: $-\text{CH}(\text{CH}_2)_2$ (cyclopropyl), cyclobutyl, cyclopentyl, or cyclohexyl. The term “cycloalkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group with one or two carbon atom as the point(s) of attachment, said carbon atom(s) forms part of one or more non-aromatic ring structures, a cyclo or cyclic structure, no

carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen.



, or are non-limiting examples of cycloalkanediyl groups. A “cycloalkane” refers to the compound $\text{H}-\text{R}$, wherein R is cycloalkyl as this term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The following

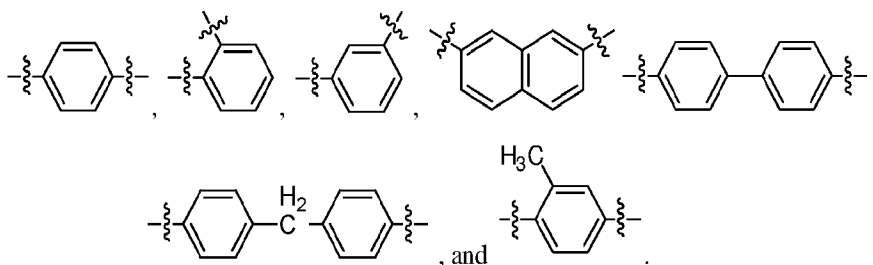
groups are non-limiting examples of substituted cycloalkyl groups: $-\text{C}(\text{OH})(\text{CH}_2)_2$,



The term “alkenyl” when used without the “substituted” modifier refers to a monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: $-\text{CH}=\text{CH}_2$ (vinyl), $-\text{CH}=\text{CHCH}_3$, $-\text{CH}=\text{CHCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$ (allyl), $-\text{CH}_2\text{CH}=\text{CHCH}_3$, and $-\text{CH}=\text{CHCH}=\text{CH}_2$. The term “alkenediyl” when used without the “substituted” modifier refers to a divalent unsaturated aliphatic group, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups, $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2-$, and $-\text{CH}=\text{CHCH}_2-$, are non-limiting examples of alkenediyl groups. It is noted that while the alkenediyl group is aliphatic, once connected at both ends, this group is not precluded from forming part of an aromatic structure. The terms “alkene” and refer to a compound having the formula $\text{H}-\text{R}$, wherein R is alkenyl as this term is defined above. A “terminal alkene” refers to an alkene having just one carbon-carbon double bond, wherein that bond forms a vinyl group at one end of the molecule. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups, $-\text{CH}=\text{CHF}$, $-\text{CH}=\text{CHCl}$ and $-\text{CH}=\text{CHBr}$, are non-limiting examples of substituted alkenyl groups.

The term “alkynyl” when used without the “substituted” modifier refers to a monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. As used herein, the term alkynyl does not preclude the presence of one or more non-aromatic carbon-carbon double bonds. The groups, $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, and $-\text{CH}_2\text{C}\equiv\text{CCH}_3$, are non-limiting examples of alkynyl groups. An “alkyne” refers to the compound $\text{H}-\text{R}$, wherein R is alkynyl. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “aryl” when used without the “substituted” modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a one or more six-membered aromatic ring structure, wherein the ring atoms are all carbon, and wherein the group consists of no atoms other than carbon and hydrogen. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3$ (ethylphenyl), naphthyl, and a monovalent group derived from biphenyl. The term “arenediyl” when used without the “substituted” modifier refers to a divalent aromatic group with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the presence of one or more alkyl, aryl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). Non-limiting examples of arenediyl groups include:

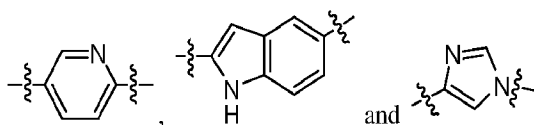


An “arene” refers to the compound $\text{H}-\text{R}$, wherein R is aryl as that term is defined above. Benzene and toluene are non-limiting examples of arenes. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “aralkyl” when used without the “substituted” modifier refers to the monovalent group $-\text{alkanediyl-aryl}$, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: phenylmethyl (benzyl, Bn) and 2-phenyl-

ethyl. When the term aralkyl is used with the “substituted” modifier one or more hydrogen atom from the alkanediyl and/or the aryl group has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, and 2-chloro-2-phenyl-eth-1-yl.

The term “heteroaryl” when used without the “substituted” modifier refers to a monovalent aromatic group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heteroaryl group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic ring or aromatic ring system. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl, pyridinyl, pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. The term “N-heteroaryl” refers to a heteroaryl group with a nitrogen atom as the point of attachment. The term “heteroarenediyl” when used without the “substituted” modifier refers to an divalent aromatic group, with two aromatic carbon atoms, two aromatic nitrogen atoms, or one aromatic carbon atom and one aromatic nitrogen atom as the two points of attachment, said atoms forming part of one or more aromatic ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). As used herein, the term does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic ring or aromatic ring system. Non-limiting examples of heteroarenediyl groups include:

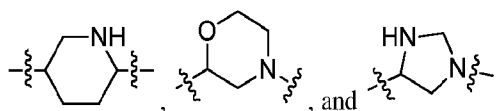


A “heteroarene” refers to the compound H–R, wherein R is heteroaryl. Pyridine and quinoline are non-limiting examples of heteroarenes. When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂.

The term “heteroaralkyl” when used without the “substituted” modifier refers to the monovalent group –alkanediyl–heteroaryl, in which the terms alkanediyl and heteroaryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of heteroaralkyls are: 2-pyridylmethyl and 2-indazolylethyl. When the term heteroaralkyl is used with the “substituted” modifier one or more hydrogen atom from the alkanediyl and/or the heteroaryl group has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂,

$-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. Non-limiting examples of substituted heteroaralkyls are: (3-chloroquinolyl)-methyl, and 2-chloro-2-thienyl-eth-1-yl.

The term “heterocycloalkyl” when used without the “substituted” modifier refers to a monovalent non-aromatic group with a carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more non-aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heterocycloalkyl group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkyl groups include aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranly, oxiranyl, and oxetanyl. The term “N-heterocycloalkyl” refers to a heterocycloalkyl group with a nitrogen atom as the point of attachment. The term “heterocycloalkanediyl” when used without the “substituted” modifier refers to an divalent cyclic group, with two carbon atoms, two nitrogen atoms, or one carbon atom and one nitrogen atom as the two points of attachment, said atoms forming part of one or more ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkanediyl groups include:



When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{NH}_2$, or $-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$ (*tert*-butoxycarbonyl, BOC).

The term “acyl” when used without the “substituted” modifier refers to the group $-\text{C}(\text{O})\text{R}$, in which R is a hydrogen, alkyl, cycloalkyl, aryl, aralkyl or heteroaryl, as those terms are defined above. The groups, $-\text{CHO}$, $-\text{C}(\text{O})\text{CH}_3$ (acetyl, Ac), $-\text{C}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}(\text{CH}_2)_2$, $-\text{C}(\text{O})\text{C}_6\text{H}_5$, $-\text{C}(\text{O})\text{C}_6\text{H}_4\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{C}_6\text{H}_5$, $-\text{C}(\text{O})$ (imidazolyl) are non-limiting examples of acyl groups. A “thioacyl” is defined in an analogous manner, except that the oxygen atom of the group $-\text{C}(\text{O})\text{R}$ has been replaced with a sulfur atom, $-\text{C}(\text{S})\text{R}$. The term “aldehyde” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a $-\text{CHO}$ group. When any of these terms are used with the “substituted” modifier one or more hydrogen atom (including a hydrogen atom directly attached the carbonyl or thiocarbonyl group, if any) has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$,

$-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups, $-\text{C}(\text{O})\text{CH}_2\text{CF}_3$, $-\text{CO}_2\text{H}$ (carboxyl), $-\text{CO}_2\text{CH}_3$ (methylcarboxyl), $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NH}_2$ (carbamoyl), and $-\text{CON}(\text{CH}_3)_2$, are non-limiting examples of substituted acyl groups.

The term “alkylamino” when used without the “substituted” modifier refers to the group $-\text{NHR}$, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylamino groups include: $-\text{NHCH}_3$ and $-\text{NHCH}_2\text{CH}_3$. The term “dialkylamino” when used without the “substituted” modifier refers to the group $-\text{NRR}'$, in which R and R' can each independently be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of dialkylamino groups include: $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, and *N*-pyrrolidinyl. The terms “alkoxyamino”, “cycloalkylamino”, “alkenylamino”, “cycloalkenylamino”, “alkynylamino”, “arylamino”, “aralkylamino”, “heteroarylamino”, “heterocycloalkylamino” and “alkylsulfonylamino” when used without the “substituted” modifier, refers to groups, defined as $-\text{NHR}$, in which R is alkoxy, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and alkylsulfonyl, respectively. A non-limiting example of an arylamino group is $-\text{NHC}_6\text{H}_5$. The term “amido” (acylamino), when used without the “substituted” modifier, refers to the group $-\text{NHR}$, in which R is acyl, as that term is defined above. A non-limiting example of an amido group is $-\text{NHC}(\text{O})\text{CH}_3$. The term “alkylimino” when used without the “substituted” modifier refers to the divalent group $=\text{NR}$, in which R is an alkyl, as that term is defined above. The term “alkylaminodiyl” refers to the divalent group $-\text{NH}-\text{alkanediyl}-$, $-\text{NH}-\text{alkanediyl}-\text{NH}-$, or $-\text{alkanediyl}-\text{NH}-\text{alkanediyl}-$. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups $-\text{NHC}(\text{O})\text{OCH}_3$ and $-\text{NHC}(\text{O})\text{NHCH}_3$ are non-limiting examples of substituted amido groups.

The term “alkoxy” when used without the “substituted” modifier refers to the group $-\text{OR}$, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-\text{OCH}_3$ (methoxy), $-\text{OCH}_2\text{CH}_3$ (ethoxy), $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$ (isopropoxy), and $-\text{OC}(\text{CH}_3)_3$ (*tert*-butoxy). The terms “cycloalkoxy”, “alkenyloxy”, “alkynyloxy”, “aryloxy”, “aralkoxy”, “heteroaryloxy”, “heterocycloalkoxy”, “acyloxy”, “alkylsilyloxy”, “alkylarylsilyloxy”, and “alkylaralkylsilyloxy”, when used without the “substituted” modifier, refers to groups, defined as $-\text{OR}$, in which R is cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, acyl, alkylsilyl, alkylarylsilyl, or alkylaralkylsilyl, respectively. The term “alkoxydiyl” refers to the divalent group $-\text{O}-\text{alkanediyl}-$, $-\text{O}-\text{alkanediyl}-\text{O}-$, or $-\text{alkanediyl}-\text{O}-\text{alkanediyl}-$. The term “alkylthio” and “acylthio” when used without the “substituted” modifier refers to the group $-\text{SR}$, in which R is an alkyl and acyl, respectively. The term “alcohol” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a hydroxy group. The term “ether” corresponds to an alkane or cycloalkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with an alkoxy or cycloalkoxy group. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “alkylsilyl” when used without the “substituted” modifier refers to a monovalent group, defined as $-\text{SiH}_2\text{R}$, $-\text{SiHRR}'$, or $-\text{SiRR}'\text{R}''$, in which R, R' and R'' can be the same or different alkyl groups, or any combination of two of R, R' and R'' can be taken together to represent an alkanediyl. The groups, $-\text{SiH}_2\text{CH}_3$, $-\text{SiH}(\text{CH}_3)_2$, $-\text{Si}(\text{CH}_3)_3$ and $-\text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$, are non-limiting examples of unsubstituted alkylsilyl groups.

5 The terms arylsilyl and aralkylsilyl refer to a monovalent group in which R, R' and R'' as shown above are aryl and aralkyl groups, respectively. The term “substituted alkylsilyl” refers $-\text{SiH}_2\text{R}$, $-\text{SiHRR}'$, or $-\text{SiRR}'\text{R}''$, in which at least one of R, R' and R'' is a substituted alkyl or two of R, R' and R'' can be taken together to represent a substituted alkanediyl. When more than one of R, R' and R'' is a substituted alkyl, they can be the same or different. Any of R, R' and R'' that are not either substituted alkyl or substituted alkanediyl, can be either alkyl,

10 either the same or different, or can be taken together to represent a alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the silicon atom. The term “aryl silyl” or “aralkylsilyl” refers to the group as defined above where at least one of R, R', or R'' is an aryl or aralkyl group as those groups are defined above. Similarly, the term “alkylaryl silyl” or “alkylaralkylsilyl” when used without the “substituted” modifier refer to monovalent groups, in which R, R' and R'' can be the same or different alkyl or aryl groups or the same

15 or different alkyl and aralkyl groups, as those terms are defined above. A substituted version of any of these groups refers to a group in which one or more of the alkyl, aryl, or aralkyl groups is substituted as those terms are defined above.

A “base” in the context of this application is a compound which has a lone pair of electron that can accept a proton. Non-limiting examples of a base can include triethylamine, a metal hydroxide, a metal alkoxide,

20 a metal hydride, or a metal alkane. An alkyllithium or organolithium is a compound of the formula $\text{alkyl}_{(\text{C} \leq 12)}\text{-Li}$. A nitrogenous base is an alkylamine, dialkylamino, trialkylamine, nitrogen containing heterocycloalkane or heteroarene wherein the base can accept a proton to form a positively charged species. For example, but not limited to, a nitrogenous base could be 4,4-dimethylpyridine, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene, diisopropylethylamine, or triethylamine. A metal alkoxide is an alkoxy group wherein rather than the oxygen

25 atom which was the point of connectivity has an extra electron and thus a negative charge which is charged balanced by the metal ion. For example, a metal alkoxide could be a sodium *tert*-butoxide or potassium methoxide. A metal carbonate is a carbonate anion with two monovalent cations or a divalent cation. Some non-limiting examples include sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, or magnesium carbonate.

30 A “fluoride source” in the context of this application is a reagent which generates or contains a fluoride ion. Some non-limiting examples include hydrofluoric acid, metal fluoride, or tetrabutylammonium fluoride.

A “linker” in the context of this application is divalent chemical group which may be used to join one or more molecules to the compound of the instant disclosure. In some embodiments, the linker contains a reactive functional group, such as a carboxyl, an amide, a amine, a hydroxy, a mercapto, an aldehyde, or a

35 ketone on each end that be used to join one or more molecules to the compounds of the instant disclosure. In some non-limiting examples, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{OCH}_2\text{CH}_2\text{NH}-$, $-\text{NHCH}_2\text{CH}_2\text{NH}-$, and $-(\text{OCH}_2\text{CH}_2)_n-$ wherein n is between 1-1000, are linkers.

A “leaving group” in the context of this application is a group which has the ability to be displaced from the molecule through nucleophilic attack. This group may also convert a hydroxyl group into a better

leaving group by stabilizing the charge on the oxygen when the atom bears a negative charge thus making the hydroxyl group more susceptible to a nucleophilic attack and displacement. In some embodiments, the leaving group may be a halogen atom such as a bromine atom or a iodine atom.

5 A "metal" in the context of this application is a transition metal or a metal of groups I or II. In some embodiments, a metal is lithium, sodium, or potassium. In other embodiments, a metal is calcium or magnesium.

An "anion" is a negatively charged cation. For example, a "monovalent anion" is a negatively charged cation with a single negative charge. Some non-limiting examples of anions include chloride, bromide, fluoride, iodide, acetate, nitrate, phosphate, sulfate, or hydroxide.

10 An "amine protecting group" is well understood in the art. An amine protecting group is a group which prevents the reactivity of the amine group during a reaction which modifies some other portion of the molecule and can be easily removed to generate the desired amine. Amine protecting groups can be found at least in Greene and Wuts, 1999, which is incorporated herein by reference. Some non-limiting examples of amino protecting groups include formyl, acetyl, propionyl, pivaloyl, *t*-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, *o*-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, *p*-toluenesulfonyl and the like; alkoxy- or aryloxycarbonyl groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), *p*-chlorobenzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, *p*-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(*p*-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, *t*-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethylloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Additionally, the "amine protecting group" can be a divalent protecting group such that both hydrogen atoms on a primary amine are replaced with a single protecting group. In such a situation the amine protecting group can be phthalimide (phth) or a substituted derivative thereof
25 wherein the term "substituted" is as defined above. In some embodiments, the halogenated phthalimide derivative may be tetrachlorophthalimide (TCphth).

30 A "hydroxyl protecting group" is well understood in the art. A hydroxyl protecting group is a group which prevents the reactivity of the hydroxyl group during a reaction which modifies some other portion of the molecule and can be easily removed to generate the desired hydroxyl. Hydroxyl protecting groups can be found at least in Greene and Wuts, 1999, which is incorporated herein by reference. Some non-limiting examples of hydroxyl protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, *t*-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, *o*-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, *p*-toluenesulfonyl and the like; acyloxy groups such as benzyloxycarbonyl (Cbz), *p*-chlorobenzyloxycarbonyl, *p*-

methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, *p*-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(*p*-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, *t*-butoxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilyl-ethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like.

A “thiol protecting group” is well understood in the art. A thiol protecting group is a group which prevents the reactivity of the mercapto group during a reaction which modifies some other portion of the molecule and can be easily removed to generate the desired mercapto group. Thiol protecting groups can be found at least in Greene and Wuts, 1999, which is incorporated herein by reference. Some non-limiting examples of thiol protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, *t*-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, *o*-nitrophenoxycarbonyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, *p*-toluenesulfonyl and the like; acyloxy groups such as benzyloxycarbonyl (Cbz), *p*-chlorobenzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, *p*-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(*p*-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, *t*-butoxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like.

An “excipient” is a pharmaceutically acceptable substance formulated along with the active ingredient(s) of a medication, pharmaceutical composition, formulation, or drug delivery system. Excipients may be used, for example, to stabilize the composition, to bulk up the composition (thus often referred to as “bulking agents,” “fillers,” or “diluent” when used for this purpose), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption, reducing viscosity, or enhancing solubility. Excipients include pharmaceutically acceptable versions of antiadherents, binders, coatings, colors, disintegrants, flavors, glidants, lubricants, preservatives, sorbents, sweeteners, and vehicles. The main excipient that serves as a medium for conveying the active ingredient is usually called the vehicle. Excipients may also be used in the manufacturing process, for example, to aid in the handling of the active substance, such as by facilitating powder flowability or non-stick properties, in addition to aiding *in vitro* stability such as prevention of denaturation or aggregation over the expected shelf life. The suitability of an

excipient will typically vary depending on the route of administration, the dosage form, the active ingredient, as well as other factors.

As used herein, the term “patient” or “subject” refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain
5 embodiments, the patient or subject is a primate. Non-limiting examples of human patients are adults, juveniles, infants and fetuses.

As generally used herein “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity,
10 irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

“Pharmaceutically acceptable salts” means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, *o*-(4-hydroxybenzoyl)benzoic acid, oxalic acid, *p*-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties*, 2002.

A “pharmaceutically acceptable carrier,” “drug carrier,” or simply “carrier” is a pharmaceutically acceptable substance formulated along with the active ingredient medication that is involved in carrying, delivering and/or transporting a chemical agent. Drug carriers may be used to improve the delivery and the effectiveness of drugs, including for example, controlled-release technology to modulate drug bioavailability, decrease drug metabolism, and/or reduce drug toxicity. Some drug carriers may increase the effectiveness of drug delivery to the specific target sites. Examples of carriers include: liposomes, microspheres (*e.g.*, made of
35

poly(lactic-co-glycolic) acid), albumin microspheres, synthetic polymers, nanofibers, protein-DNA complexes, protein conjugates, erythrocytes, virosomes, and dendrimers.

A “stereoisomer” or “optical isomer” is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs.

5 “Enantiomers” are stereoisomers of a given compound that are mirror images of each other, like left and right hands. “Diastereomers” are stereoisomers of a given compound that are not enantiomers. Chiral molecules contain a chiral center, also referred to as a stereocenter or stereogenic center, which is any point, though not necessarily an atom, in a molecule bearing groups such that an interchanging of any two groups leads to a stereoisomer. In organic compounds, the chiral center is typically a carbon, phosphorus or sulfur atom, though

10 it is also possible for other atoms to be stereocenters in organic and inorganic compounds. A molecule can have multiple stereocenters, giving it many stereoisomers. In compounds whose stereoisomerism is due to tetrahedral stereogenic centers (*e.g.*, tetrahedrally substituted carbon atoms), the total number of hypothetically possible stereoisomers will not exceed 2^n , where n is the number of tetrahedral stereocenters. Molecules with symmetry frequently have fewer than the maximum possible number of stereoisomers. A 50:50 mixture of enantiomers

15 is referred to as a racemic mixture. Alternatively, a mixture of enantiomers can be enantiomerically enriched so that one enantiomer is present in an amount greater than 50%. Typically, enantiomers and/or diastereomers can be resolved or separated using techniques known in the art. It is contemplated that that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its (*R*) form, (*S*) form, or as a mixture of the (*R*) and (*S*) forms, including racemic and non-racemic

20 mixtures. As used herein, the phrase “substantially free from other stereoisomers” means that the composition contains $\leq 15\%$, more preferably $\leq 10\%$, even more preferably $\leq 5\%$, or most preferably $\leq 1\%$ of another stereoisomer(s).

V. Examples

The following examples are included to demonstrate preferred embodiments of the disclosure. It should

25 be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the disclosure, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

30

EXAMPLE 1 – Enantioselective Synthesis of Viridicatumtoxin and Analogs Thereof

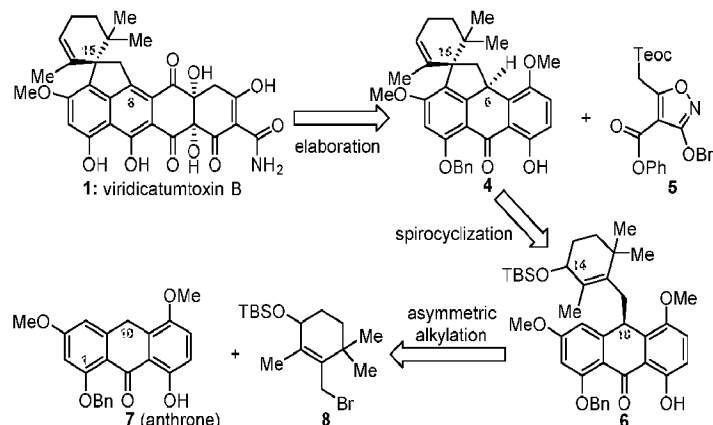
A. Asymmetric Alkylation of Anthrones.

Scheme 1 below describes in retrosynthetic format the strategy employed in earlier first total synthesis of viridicatumtoxin B (**1**) in which the target molecule was traced back to key building blocks **5**, **7** and **8** through

35 advanced intermediates **4** and **6**, with the latter being the first key chiral compound enroute to **1**. The asymmetric generation of intermediate **6** through alkylation of anthrone **7** with cyclic allylic bromide **8**, therefore, became the key challenge for an asymmetric route to viridicatumtoxin B and its analogues. This challenge was expected to be difficult not only due to the potential propensity of alkylation product **6** to C10 (anthrone numbering)

racemization under the required basic conditions but also because of its perceived sensitivity to isomerize under the Lewis acid-mediated spirocyclization conditions to form the next advanced intermediate, chiral pentacyclic compound **4** (viridicatumtoxin numbering). Although numerous asymmetric alkylations have been reported (Trost *et al.*, 2006; Trost, 2004; Trost and Crawley, 2003; Trost and Van Vranken, 1996; Trost, 1996; Maruoka and Ooi, 2003; Ooi and Maruoka, 2007; Trost and Bunt, 1994; Shih *et al.*, 2010; Liu *et al.*, 2011; Provencher *et al.*, 2011; Ceban *et al.*, 2015), a practical asymmetric alkylation of anthrones **7** was not available.

Scheme 1: Asymmetric Total Synthesis of Viridicatumtoxin B



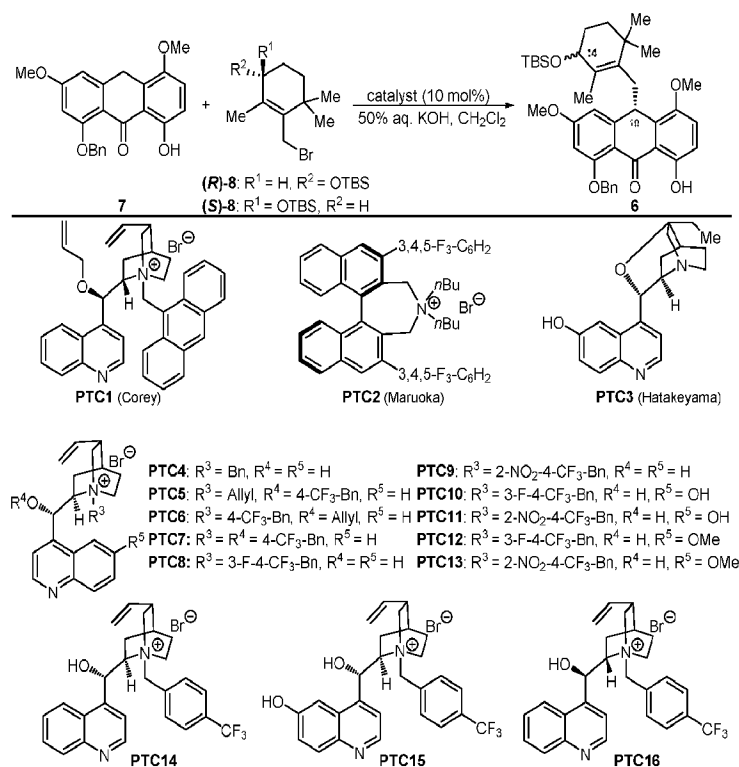
Focusing on known asymmetric alkylation reactions (Trost *et al.*, 2006; Trost, 2004; Trost and Crawley, 2003; Trost and Van Vranken, 1996; Trost, 1996; Maruoka and Ooi, 2003; Ooi and Maruoka, 2007; Trost and Bunt, 1994; Shih *et al.*, 2010; Liu *et al.*, 2011; Provencher *et al.*, 2011; Ceban *et al.*, 2015), the initial studies pointed to phase transfer catalysts as promising for further studies. Brief exploration of phase transfer catalysts **PTC1** (Corey *et al.*, 1997; Corey *et al.*, 1998) and **PTC2** (Kitamura *et al.*, 2005) and chiral base catalyst **PTC3** (Iwabuchi *et al.*, 1999) identified the Corey catalyst (**PTC1**) as the most practical and efficient to pursue as a lead scaffold for further optimization (see Table 1, entries 1–3). Thus, following this pathpointing observation, a series of catalysts [newly synthesized: **PTC5**, **PTC7–PTC13** and **PTC15**; previously reported: **PTC4** (Lee and Wong, 1994; Lian *et al.*, 2010), **PTC6** (Kobbelgaard *et al.*, 2006; Liang *et al.*, 2014), **PTC14** (Zeng *et al.*, 2013; Adam *et al.*, 2002; Xie *et al.*, 2014), and **PTC16** (Johnston *et al.*, 2015; Li *et al.*, 2013), Table 1, entries 4–18; for further catalysts synthesized and tested] were tested for their efficiency in the anthrone alkylation reaction with racemic [(*R,S*)-] or enantiopure [(*R*)- or (*S*)-] allylic bromide **8** in a two-phase solvent system (50% aq. KOH:CH₂Cl₂) at –78 to 0 °C. As seen in Table 1, the best results were obtained with **PTC15** and the (*R*)-enantiomer of allylic bromide **8** [(*R*)-**8**, 99% substrate conversion, 75% yield, 89:11 dr, entry 17], although the reaction with (*R,S*)-**8** also performed well (99% substrate conversion, 75% yield and 86:14 dr, entry 15). The performance of **PTC9** and **PTC14** were also of note (entries 9 and 14, respectively, Table 1). The significant difference in diastereoselectivity observed with the (*S*)-enantiomer of **8** [(*S*)-**8**, entry 16, 83:17 dr] drew considerable interest. The ability to synthesize the antipode of alkylation product **6** was demonstrated by using the (*S*)-enantiomer of allylic bromide **8** and catalyst **PTC16** (pseudo-enantiomer of **PTC14**, prepared from cinchonidine, 99% substrate conversion, 76% yield, 13:87 dr, entry 18, Table 1).

The superiority of catalysts **PTC8**, **PTC9**, **PTC15** and **PTC16** (Table 1, entries 8, 9, 15–18), all of which include an electron withdrawing group on their benzyloxy residue, as opposed to relatively electron rich catalysts carrying a benzyloxy substituent (*e.g.* **PTC4**, entry 4, Table 1), is in line with Maruoka's work (Nelson

et al., 2001). This trend is further corroborated with the observed superiority of catalysts **PTC39**, **PTC40** and **PTC41** (all of which contain fluorine atoms on their benzyloxy residue, see Example 3) over **PTC38**, whose benzyloxy moiety includes an electron rich residue (*e.g.*, Me, see Example 3).

Table 1. Catalyst Optimization of Alkylation of Anthrone 7 with Allylic Bromide 8 [(*R*) and/or

5 (*S*)]^a



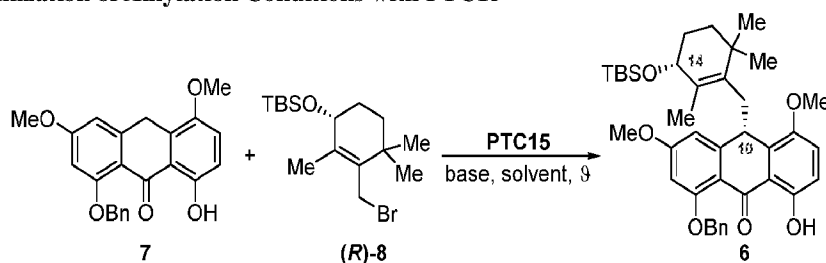
Entry	Catalyst	8 (R ¹ , R ²) ^b	Conv. (%)	Yield (%)	dr (%) ^c
1	PTC1	(<i>S</i>) and (<i>R</i>)	>99	78	62:38
2	PTC2	(<i>S</i>) and (<i>R</i>)	90	70	61:39
3	PTC3	(<i>S</i>) and (<i>R</i>)	>99	75	55:45
4	PTC4	(<i>S</i>) and (<i>R</i>)	>99	77	63:37
5	PTC5	(<i>S</i>) and (<i>R</i>)	>99	76	58:42
6	PTC6	(<i>S</i>) and (<i>R</i>)	>99	74	60:40
7	PTC7	(<i>S</i>) and (<i>R</i>)	>99	76	62:38
8	PTC8	(<i>S</i>) and (<i>R</i>)	>99	73	82:18
9	PTC9	(<i>S</i>) and (<i>R</i>)	80	70	83:17
10	PTC10	(<i>S</i>) and (<i>R</i>)	>99	72	80:20
11	PTC11	(<i>S</i>) and (<i>R</i>)	>99	70	79:21
12	PTC12	(<i>S</i>) and (<i>R</i>)	>99	72	58:42
13	PTC13	(<i>S</i>) and (<i>R</i>)	>99	75	64:36
14	PTC14	(<i>S</i>) and (<i>R</i>)	>99	76	84:16
15	PTC15	(<i>S</i>) and (<i>R</i>)	>99	75	86:14
16	PTC15	(<i>S</i>)	>99	75	83:17
17	PTC15	(<i>R</i>)	>99	75	89:11

Entry	Catalyst	8 (R ¹ , R ²) ^b	Conv. (%)	Yield (%)	dr (%) ^c
18	PTC16 ^e	(S)	>99	76	13:87

^aReaction conditions: anthrone **7** (0.10 mmol), allylic bromide **8** (0.11 mmol), PTC cat. (10 mol%), CH₂Cl₂ (0.9 mL), 50% aq. KOH (0.3 mL), -78 to 0 °C, 8 h. ^bAllylic bromides (*R*)-**8** and (*S*)-**8** were prepared through a standard sequence (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014) involving CBS reduction (Corey *et al.*, 1987) of an intermediate enone. ^cThe diastereoisomeric ratio (dr) was determined by HPLC using a chiralPak AD-H column, the dr ratios for entries 1–15 were determined from the HPLC peak areas corresponding to (10*S*)-6:(10*R*)-6. ^dPTC16 is the pseudo-enantiomer of PTC14.

Striving for higher asymmetric induction and efficiency, and beyond catalyst and alkylating agent absolute configuration optimization, the effect of reaction conditions and catalyst loading on the alkylation of anthrone **7** with TBS-protected alkylating agent (*R*)-**8** and catalyst **PTC15** was then investigated. Table 2 summarizes the results of this study that involved changes in the aqueous base, organic solvent, temperature, reaction time and catalyst loading. Initial experiments (entries 1–6, Table 2) led to the identification of 40% aq. Cs₂CO₃ and CH₂Cl₂ as the optimal base and solvent, respectively (entry 5, 0 °C, 10 mol% cat., 75% yield, 92:8 dr, Table 2). Changing the solvent from CH₂Cl₂ to (CH₂)₂Cl₂ increased the dr slightly (93:7, entry 7, Table 2), while decreasing the temperature steadily from 0 to -30 °C led to further improvements in the dr with proportional increases in reaction time as expected (93:7; 94:6; 95:5; entries 12–14, respectively, Table 2). Stepwise decrease of catalyst loading from 10 to 0.1 mol% resulted in a slight increase of efficiency, in a relative inverse relationship with the reaction time (95:5 to 96:4 dr, entries 14 to 16, Table 2). The lower yield (due to decreased rate and conversion) reflected in entry 16 (Table 2, 15% yield) with 0.1 mol% catalyst loading provided an unacceptable limit, thereby leading the 0.5 mol% catalyst loading as the most practical with regard to reaction rate, yield, and diastereoselectivity for future studies (72% yield, 95:5 dr, 40% aq. Cs₂CO₃, (CH₂)₂Cl₂, -30 °C, 180 h, entry 17, Table 2).

Table 2. Optimization of Alkylation Conditions with PTC15^a



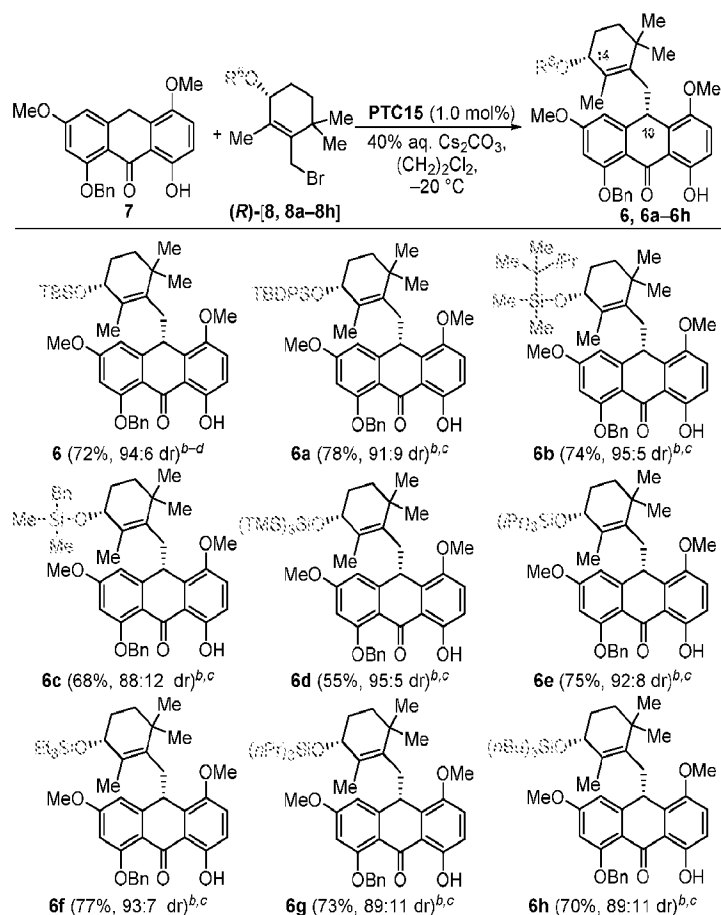
Entry	Base (aq. solution)	Solvent	9 (°C)	Time (h)	Cat. ^b (mol%)	Yield (%)	dr ^c
1	50% KOH	CH ₂ Cl ₂	0	8	10	77	89:11
2	50% NaOH	CH ₂ Cl ₂	0	8	10	77	89:11
3	50% Cs ₂ CO ₃	CH ₂ Cl ₂	0	8	10	77	91:9
4	50% K ₂ CO ₃	CH ₂ Cl ₂	0	8	10	75	91:9
5	40% Cs ₂ CO ₃	CH ₂ Cl ₂	0	8	10	75	92:8
6	30% Cs ₂ CO ₃	CH ₂ Cl ₂	0	8	10	73	91:9
7	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	0	8	10	72	93:7
8	40% Cs ₂ CO ₃	CHCl ₃	0	8	10	60	85:15
9	40% Cs ₂ CO ₃	CCl ₄	0	8	10	50	81:19
10	40% Cs ₂ CO ₃	PhMe	0	8	10	78	84:16
11	40% Cs ₂ CO ₃	EtOAc	0	8	10	65	78:22
12	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-10	24	10	72	93:7
13	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-20	72	10	72	94:6
14	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-30	180	10	72	95:5
15	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-30	180	1	72	95:5

Entry	Base (aq. solution)	Solvent	9 (°C)	Time (h)	Cat. ^b (mol%)	Yield (%)	dr ^c
16 ^a	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-30	200	0.1	15	96:4
17 ^d	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-30	180	0.5	72	95:5
18	40% Cs ₂ CO ₃	(CH ₂) ₂ Cl ₂	-20	72	1	72	94:6

^aReaction conditions: anthrone **7** (0.10 mmol), allylic bromide (**R**)-**8** (0.11 mmol), **PTC15**, solvent (0.9 mL), aq. base solution (0.3 mL). ^bCat. = catalyst loading. ^cThe dr [(10S)-**6**:(10R)-**6**] was determined by HPLC using a chiralPak AD-H column, see Example 3. ^dReaction was run on 5 mmol scale (anthrone). For further studies on possible C10 racemization of the alkylation product under basic conditions, see Example 3.

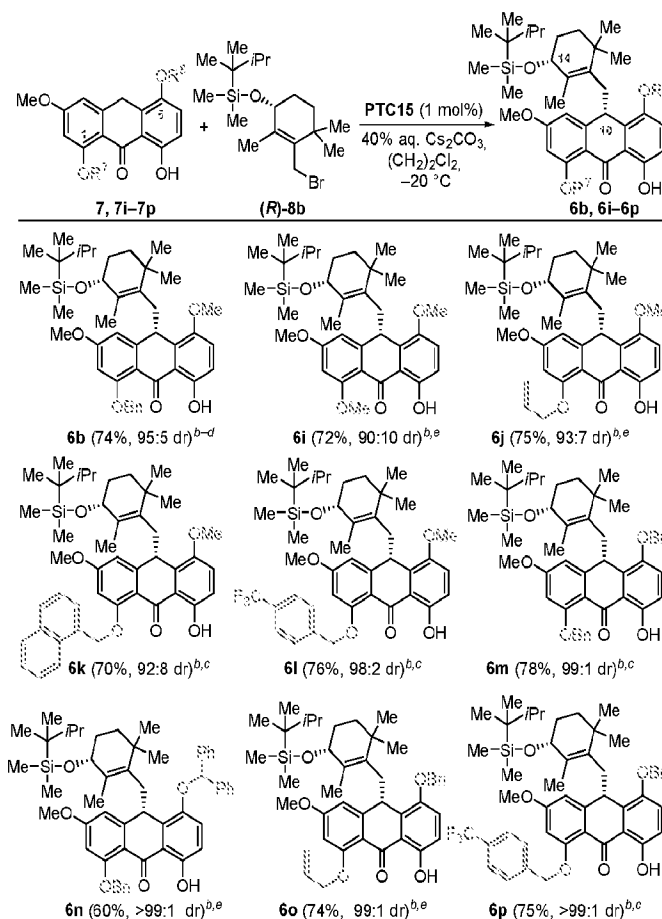
5 Inspired by the effect of the chirality of the alkylating agent on the diastereoselectivity of the anthrone alkylation reaction as described above (Table 1) investigations were carried out on a series of allylic bromides (**R**)-**8** varying in size of silyl protecting groups. For this investigation the catalyst **PTC15** and the conditions of entry 18 rather than those of entry 17 (Table 2) due to the shorter reaction time (for convenience) were used. As shown in Table 3, the results of this study indicated a correlation between the bulkiness of the silyl protecting group and asymmetric induction. Thus, the most effective groups inducing the highest diastereoselectivities were those leading to products **6d** [tris(trimethylsilyl)silyl: 95:5 dr, 55% yield], **6b** (hexyldimethylsilyl: 95:5 dr, 74% yield), and **6** (*tert*-butyldimethylsilyl: 94:6 dr, 72% yield). Because of the lower yield of the reaction with tris(trimethylsilyl)silyl-protected allylic bromide (**R**)-**8d**, alkylating agents (**R**)-**8b** (hexyldimethylsilyl) and (**R**)-**8** (*tert*-butyldimethylsilyl) were chosen as the most attractive for further optimization.

15 The absolute configuration of substituted anthrone **6a** (m.p. 165–166 °C) resulting from the diastereoselective alkylation of anthrone **5**, allylic bromide (**R**)-**8a** and **PTC15** as described in Scheme 2 was determined by X-ray crystallographic analysis (see ORTEP, FIG. 2) (CCDC 1447911 contains the supplementary crystallographic data of **6a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre). The crystallization of **6a** allowed its absolute configuration
20 assignment to be determined at this point, while all other products in Scheme 2 were foams in nature.

Scheme 2: Asymmetric Alkylation with Different Allylic Bromides^a

^aReaction conditions: anthrone **7** (0.10 mmol), allylic bromides **(R)-[8, 8a-8h]** (0.11 mmol), **PTC15** (1 mol%), $(\text{CH}_2)_2\text{Cl}_2$ (0.9 mL), 40% aq. Cs_2CO_3 (0.3 mL), -20°C , 72 h. ^bIsolated yield. ^cThe dr [(**10S**):(**10R**)] was determined by HPLC using a chiralPak AD-H column, see SI. ^dAlso shown in Table 2, this reaction was repeated in this study as a further confirmation of its diastereoselectivity. TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

Finally, the C1 and C5 substituent effects on the diastereoselectivity of the anthrone alkylation using the thexyldimethylsilyl-protected bromide **(R)-8b**, anthrones **7, 7i-7p**, and **PTC15** was explored under the optimized conditions as shown in Table 4. These studies revealed that substituents at the C1 position of the anthrone substrates smaller than OBn (*e.g.*, **6b**, 95:5 dr) resulted in decreased diastereoselectivities (*e.g.*, **6i**: 90:10 dr; **6j**: 93:7 dr) while larger substituents at this position led to increased diastereoselectivities (*e.g.* **6k**: 92:8 dr; **6l**: 98:2 dr). The significant increase in diastereoselectivity for product **6l** carrying the *p*-trifluoromethyl benzyloxy group was notable. When taken together with the finding that a benzyloxy group at C5 (*e.g.*, **6m**), instead of methoxy, increased the diastereoselectivity to 99:1 dr, the reaction led to increased improvements in the diastereoselectivity. Thus, the highest diastereoselectivities were obtained for the combinations of anthrone substrates (**7n**, **7o**, **7p**) and alkylating agent **(R)-8b**, which led to highly enantioenriched products **6n** (>99:1 dr), **6o** (99:1 dr), and **6p** (>99:1 dr) as shown in Scheme 3.

Scheme 4: Asymmetric Alkylation with Different Anthrones^a

^aReaction conditions: anthrones **7**, **7i-7p** (0.10 mmol), **(R)-8b** (0.11 mmol), **PTC15** (1 mol%), $(\text{CH}_2)_2\text{Cl}_2$ (0.9 mL), 40% aq. Cs_2CO_3 (0.3 mL), -20°C , 72 h. ^bIsolated yield. ^cThe dr [(10S):(10R)] was determined by HPLC using chiralPak AD-H column, see Example 3. ^dAlso shown in Scheme 2, this reaction was repeated in this study as a further confirmation of its diastereoselectivity. ^eThe dr was determined by HPLC using chiralPak AD-H column after benzylation of the product, see Example 3.

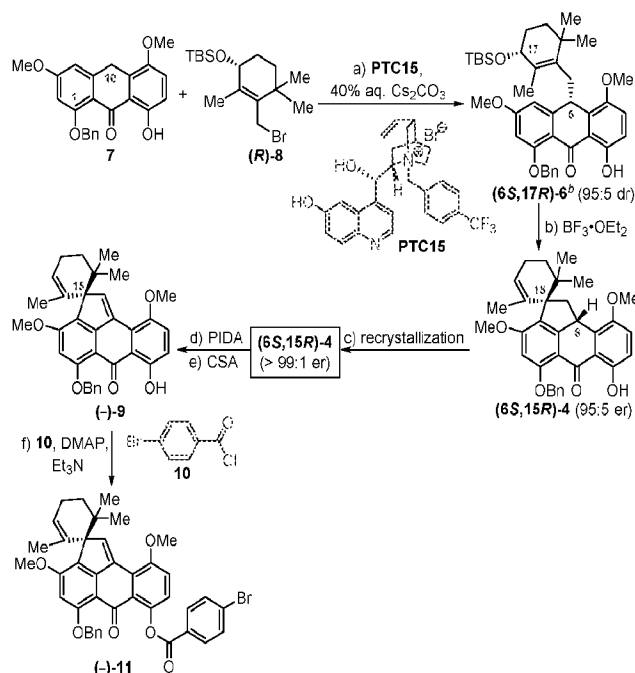
B. Enantioselective Total Synthesis and Absolute Configuration of (–)-Viridicatumtoxin B.

With an efficient and highly enantioselective synthesis of 10-substituted anthrones, the total synthesis of enantiopure viridicatumtoxin B was developed in an attempt to determine its absolute configuration. Given that the literature reports on the structures of viridicatumtoxin A (**2**, FIG. 1: absolute configuration confirmed by X-ray crystallographic analysis) [Silverton *et al.*, 1982] and spirohexaline (Inokoshi *et al.*, 2013) (**3**, reported structure, FIG. 3) suggested opposite absolute configurations for these two siblings, the absolute configuration of viridicatumtoxin B to target first was of limited interest. Since the asymmetric synthesis of anthrones revealed a higher diastereoselectivity for **PTC15** (leading to the corresponding C10-substituted anthrones, see Table 1) than **PTC16** (leading to the antipodal enantiomer), the former was employed as a means to reach one of the enantiomers of viridicatumtoxin B (**1**).

To this end, substrate anthrone **7**, alkylating agent allylic bromide **(R)-8**, and catalyst **PTC15** was adopted in an attempt to construct the first chiral intermediate (**6S,17R**)-**6** and convert it stereospecifically to the pending intermediate, spiropentacycle (**6S,15R**)-**4**, enroute to viridicatumtoxin B (Scheme 5). The reaction was carried out with caution given the sensitivity of the substrate and the conditions involved in this spirocyclization. As shown in Scheme 1, the reaction of anthrone **7** (3.01 g, 8.00 mmol) with allylic bromide

(*R*)-**8** (3.06 g, 8.80 mmol) under the influence of **PTC15** (0.5 mol%) was carried out on gram scale, delivering the expected substituted anthrone (**6*S*,17*R*)-**6** in 72% yield and 95:5 dr. The latter was subjected to optimized Lewis acid-mediated spirocyclization conditions ($\text{BF}_3 \cdot \text{Et}_2\text{O}$, 5 mol%) to afford spiropentacycle (**6*S*,15*R*)-**4** in 74% yield with no loss of enantiopurity (95:5 er, see details in Example 3). Recrystallization of (**6*S*,15*R*)-**4** from hexanes: CH_2Cl_2 (50:1) led to further enantioenrichment of this intermediate (> 99:1 er). After unsuccessful attempts to prepare a crystalline, heavy atom-containing derivative of (**6*S*,15*R*)-**4** for absolute configuration determination purposes (including the newly formed spirocenter), the latter first was subjected to the action of diacetoxyiodo-benzene (PIDA) and then to camphorsulfonic acid (CSA) in $\text{MeOH}:\text{CH}_2\text{Cl}_2$, conditions that led to *p*-quinomethide (–)-**9** (via the corresponding dimethoxyketal) in 81% overall yield. Treatment of (–)-**9** with *p*-bromobenzoyl chloride under basic conditions furnished crystalline derivative (–)-**11** (m.p. 220–221 °C), whose single crystal X-ray crystallographic analysis (see ORTEP, **FIG. 4**) [CCDC 1503479 contains the supplementary crystallographic data of **11** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre] revealed that indeed the single stereocenter (C15, viridicatumtoxin numbering) within intermediate (–)-**9**, to be converted to virididatumtoxin B, was of the shown chirality. Chiral HPLC analysis confirmed its homogeneity as a single enantiomer (see details in Example 3). This absolute configuration corresponds to that suggested for spirohexaline (**3**) (Inokoshi *et al.*, 2013), rather than that determined for viridicatumtoxin A (**2**) (Silverton *et al.*, 1982).********

Scheme 5: Enantioselective Synthesis of the BCDEF Fragment (6*S*, 15*R*)-4** of (–)-Viridicatumtoxin B [(–)-**1**] and Its Absolute Configuration^a**

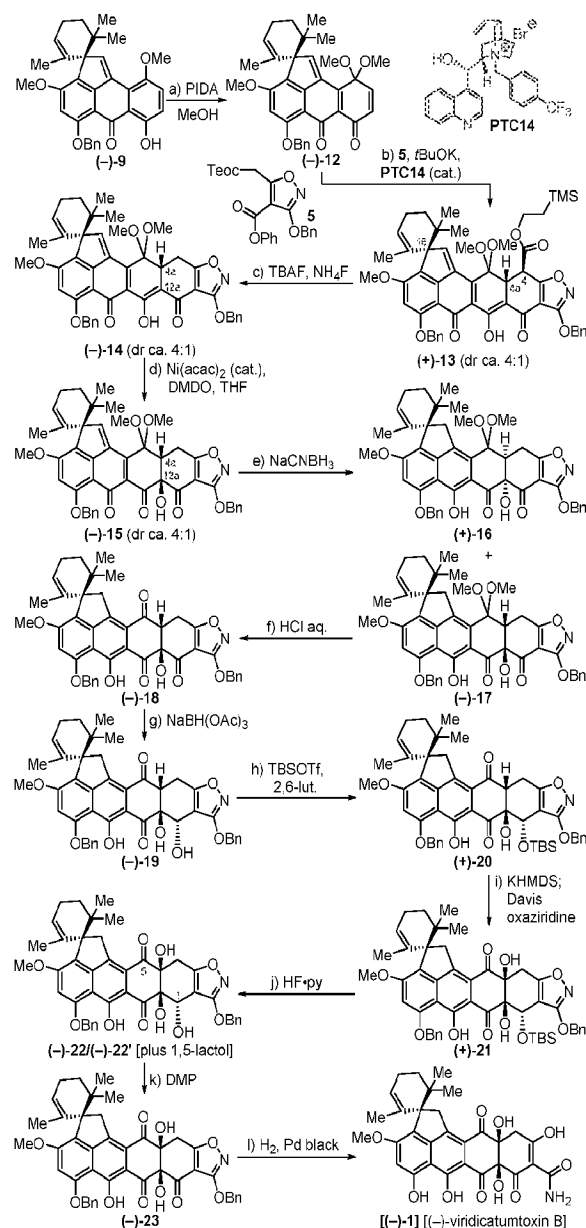


^aReagents and conditions: (a) **7** (3.01 g, 8.00 mmol scale), **PTC15** (0.5 mol%) 40% aq. Cs_2CO_3 , $(\text{CH}_2)_2\text{Cl}_2$, –30 °C, 10 days, 72%, 95:5 dr; (b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.05 equiv), CH_2Cl_2 , –78 to 0 °C, 30 min, 74%, 95:5 er; (c) hexanes: CH_2Cl_2 (50:1), 91%, >99:1 er; (d) PIDA (1.2 equiv), $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (1:1), 0 °C, 30 min, 25 °C, 30 min; (e) CSA (0.07 equiv), CH_2Cl_2 , 0 °C, 5 min, 81% for two steps; (f) **10** (5.0 equiv), DMAP (10 equiv), Et_3N (30 equiv), CH_2Cl_2 , 25 °C, 6 h, 95%. Note: to avoid confusion, the numbering on (**6*S*,17*R*)-**6**, (**6*S*,15*R*)-**4** and (–)-**9** in this Scheme and **FIG. 4** is based on the viridicatumtoxin numbering, as opposed to the carbon numbering of compound (**10*S*,14*R*)-**6** (see Table 1), which is the same compound as (**6*S*,17*R*)-**6**, but numbered based on the anthrone numbering.********

Without wishing to be bound by any theory, it is believed that the faithful transfer of absolute configuration from C6 (viridicatumtoxin numbering) in intermediate **(6*S*,17*R*)-6** to C15 in **(6*S*,15*R*)-4** is the consequence of the carbonium-mediated spirocyclization that requires attack of the C7 position on the aromatic ring onto C15 carbonium ion from the “top” side of a sterically controlled transition state (**A**: preferred; **B**: sterically congested), in which the *gem*-dimethyl groups play a non-negotiable steric control (see **FIG. 5**).

To obtain both enantiomeric forms of viridicatumtoxin B prompted further development with this enantiomer of key building block **(-)-9**, whose absolute configuration has been just determined, and whose single stereocenter (15*R*) was destined to control the stereochemistry of all others en route to the targeted molecule. This analysis also allowed an opportunity along with a way to optimize the process from the original one that delivered racemic viridicatumtoxin B (**1**) (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). Scheme 6 summarizes the optimized synthesis of **(-)-viridicatumtoxin B [(-)-1]** starting with enantiopure precursor **(-)-9**.

Scheme 6: Total Synthesis of Enantiopure **(-)-Viridicatumtoxin B [(-)-1]^a**



5 "Reagents and conditions: (a) PIDA (1.2 equiv), MeOH:CH₂Cl₂ (10:1), 25 °C, 1.5 h, 86%; (b) **5** (1.1 equiv), *t*BuOK (1.2 equiv), **PTC14** (0.01 equiv), toluene, -50 °C, 48 h, 88%, 4:1 dr; (c) TBAF (10 equiv), NH₄F (20 equiv), degassed THF, 25 °C, 5 min, 87%, 4:1 dr; (d) [Ni(acac)₂] (0.2 equiv), DMDO (3.0 equiv), THF, -78 °C, 3 h, 52% (4:1 dr, 72% brsm), 28% recovered (**-14**); (e) NaCNBH₃ (4 equiv), THF, -78 °C, 1.5 h, 48% for (**-17**), 12% for (**+16**), chromatographically separated; (f) 2 N aq. HCl, THF, 25 °C, 5 h, quant.; (g) NaBH(OAc)₃ (1.2 equiv), EtOAc:acetone (1:1), 40 °C, 2 h, 46%; (h) TBSOTf (4 × 10 equiv), 2,6-lutidine (4 × 15 equiv), CH₂Cl₂, 0 to 25 °C for four times, totaling 2 h, 76%; (i) KHMDS (3.4 equiv), THF, -78 °C, 1 h; then freshly prepared Davis oxaziridine (3.9 equiv), -78 °C, 2 h, 32% of (**+21**) (55% brsm) + 42% recovered (**+20**); (j) HF•pyridine (excess, added at 0 °C in four portions), MeCN, 0 to 55 °C for four times, totaling 20 h, 72% (product **22** exists in equilibrium with its 1,5-lactol isomeric form); (k) DMP solution in CH₂Cl₂ (0.3 M, 1.8 equiv, added in two portions at 0 °C), (CH₂)₂Cl₂, 0 to 50 °C for two times, totaling 2 h, 82%; (l) H₂, Pd black (4.9 equiv), 1,4-dioxane:MeOH (1:1), 25 °C, 10 min, 96%.

Thus, dearomatization of (**-9**) with PIDA in MeOH/CH₂Cl₂ furnished, in 90% yield, dimethoxy semi-quinone (**-12**). In an effort to improve the low diastereoselectivity (ca 2:1 dr) (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014) of the coupling of racemic **12** with oxazoline **5**, the reaction (*t*BuOK, -50 °C, 48 h) was performed in the presence of chiral catalyst **PTC14** in the hope that the chiral catalyst would add a degree of stereocontrol. The formation of the expected heptacycle product (**+13**), was observed in 88% yield and with ca 4:1 dr, as opposed to 91% yield and ca 2:1 dr in the original procedure, a significant improvement since the major diastereoisomer was the desired one as shown in Scheme 6. Complexation of ligand **PTC14** with the initially formed anion of oxazoline **5** followed by preferred attack on substrate (**-12**) from the "bottom" side may explain the observed diastereoselectivity. The diastereoselectivity described for this reaction in this reaction refers to the C15 and C4/C4a stereocenters with the latter being of the *syn* configuration with respect to the H-residue on C4a. The 4:1 mixture of Teoc derivative (**+13**) was transformed to the decarboxylated ketoenol (**-14**) as previously described (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). The hydroxylation of (**-14**) was improved in terms of both yield and diastereoselectivity from the original (36%, 2:1 dr, 60% based on recovered starting material) through optimized conditions [THF, 0.2 equiv Ni(acac)₂, 3.0 equiv DMDO, THF, -78 °C, 3 h, 52%, 4:1 dr, 72% based on recovered starting material]. Without wishing to be bound by any theory, it is believed that this improvement may be attributed to increased reactivity of Ni(acac)₂ in THF as solvent (as opposed to the originally used CH₂Cl₂), an effect that resulted in a cleaner and faster reaction. The reduction of (**-15**) (4:1 diastereomeric mixture) with NaCNBH₃ allowed convenient separation of the resulting isomeric products (**+16**) and (**-17**) through standard chromatographic techniques, with the latter now obtained from (**-13**) with improved overall diastereoselectivity (ca 4:1) as opposed to ca 2:1 in the earlier route (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). The ketal hydrolysis of the major isomer (**-17**) with aqueous HCl proceeded well to afford hydroxy triketone (**-18**), whose regioselective reduction with NaBH(OAc)₃ furnished dihydroxy diketone (**-19**) (46% yield). Optimization of the conditions of the ensuing silylation of the dihydroxy diketone (**-19**) with TBSOTf and 2,6-lutidine led to a 15% improvement in the yield of TBS-ether (**+20**) (76% vs 61% [Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014]). Finally, the crucial hydroxylation of (**+20**) was enhanced over the original procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014) (32% yield, 55% based on 42% recovered starting material) by optimization of conditions such as utilizing freshly prepared Davis oxaziridine reagent. The recruiting steps proceeded as previously reported for the racemic series (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014) to provide enantiopure (**-**)-viridicatumtoxin B [(**-1**)] through intermediates (**-22**) (HF•py, 72% yield; existing as an equilibrium mixture with its 1,5-lactol isomeric form (**-22'**) and (**-23**). The latter intermediate was obtained in 82% yield (as compared to 66% for the previous procedure (Nicolaou *et al.*, 2013;

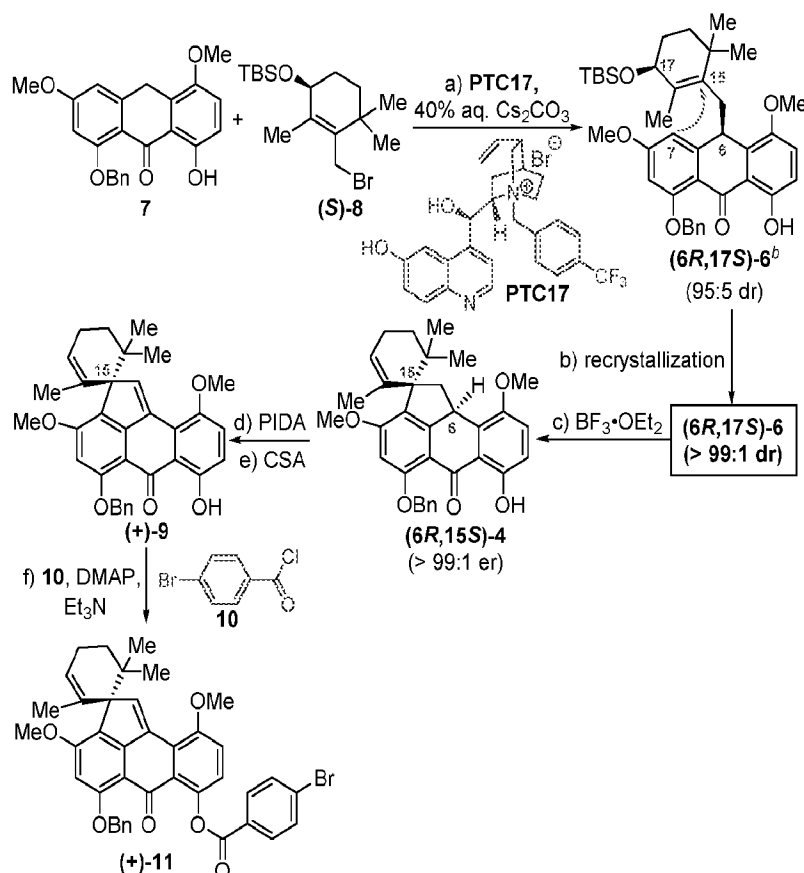
Nicolaou *et al.*, 2014) by adding the DMP as a solution in CH₂Cl₂ slowly and in portions. Finally, exposure of precursor (–)-**23** to hydrogenolysis conditions (H₂, Pd black) furnished the desired viridicatumtoxin B, whose levorotatory nature ($[\alpha]_D^{22} = -116$, $c = 0.1$, EtOH) led to its absolute configuration assignment as the enantiomer [(–)-**1**] of the natural product. Besides pointing to the absolute configuration of natural viridicatumtoxin B, without wishing to be bound by any theory, it is believed that this observation also cast doubts over the depicted absolute configuration of spirohexaline in the isolation paper (Inokoshi *et al.*, 2013).

C. Enantioselective Total Synthesis and Absolute Configuration of (+)-Viridicatumtoxin B.

With an enantioselective and improved synthetic route at hand, the road to what was sure to be the correct enantiomer of viridicatumtoxin B was now open. For optimum results, in addition to anthrone **7**, the (*S*)-enantiomer of allylic bromide **8**, [(*S*)-**8**], and the new catalyst **PTC17** (derived from quinine), the latter being the pseudo-enantiomer of **PTC15** (derived from quinidine), was used rather than **PTC16** that was used in the methodology development study described above (see Table 1). Equipped with the phenolic moiety on its quinoline domain, **PTC15** proved its superiority over **PTC16**, which lacks this phenolic group, as seen in Table 1 (entries 17, 18). This crucial observation prompted us to synthesize **PTC17** (see Scheme 3; for details of the synthesis, see Example 3), as we expected it to perform better than **PTC16** in the anthrone alkylation step.

Indeed and as shown in Scheme 7, catalyst **PTC17** performed well in ensuring high diastereoselectivity in the alkylation of anthrone **7** (6.02 g scale, 16.0 mmol) with allylic bromide (*S*)-**8**, affording alkylated anthrone (**6R,17S**)-**6** in 72% yield and 95:5 dr (as opposed to 87:13 dr obtained with **PTC16**, see Table 1, entry 18). The obtained product was purified by recrystallization from hexanes; the racemate crystallized out of the solution and the enriched material [(**6R,17S**)-**6**] was recovered from the mother liquor. The enriched starting material was then subjected to the developed spirocyclization reaction conditions [BF₃•Et₂O (cat.)] furnishing desired pentacycle (**6R,15S**)-**4** as expected. The absolute configuration of this intermediate was determined by conversion to its *p*-bromobenzoate derivative (+)-**11**, obtained via intermediate (+)-**9**, as summarized in Scheme 7. The X-ray crystallographic analysis (see ORTEP representation, FIG. 6) of (+)-**11** (m.p. 220–221 °C) confirmed its (*S*) absolute configuration as expected from the results shown in Scheme 7 for its enantiomer.

Scheme 7: Enantioselective Synthesis of the BCDEF Fragment (6*R*,15*S*)-4 of (+)-Viridicatumtoxin B and Its Absolute Configuration^a



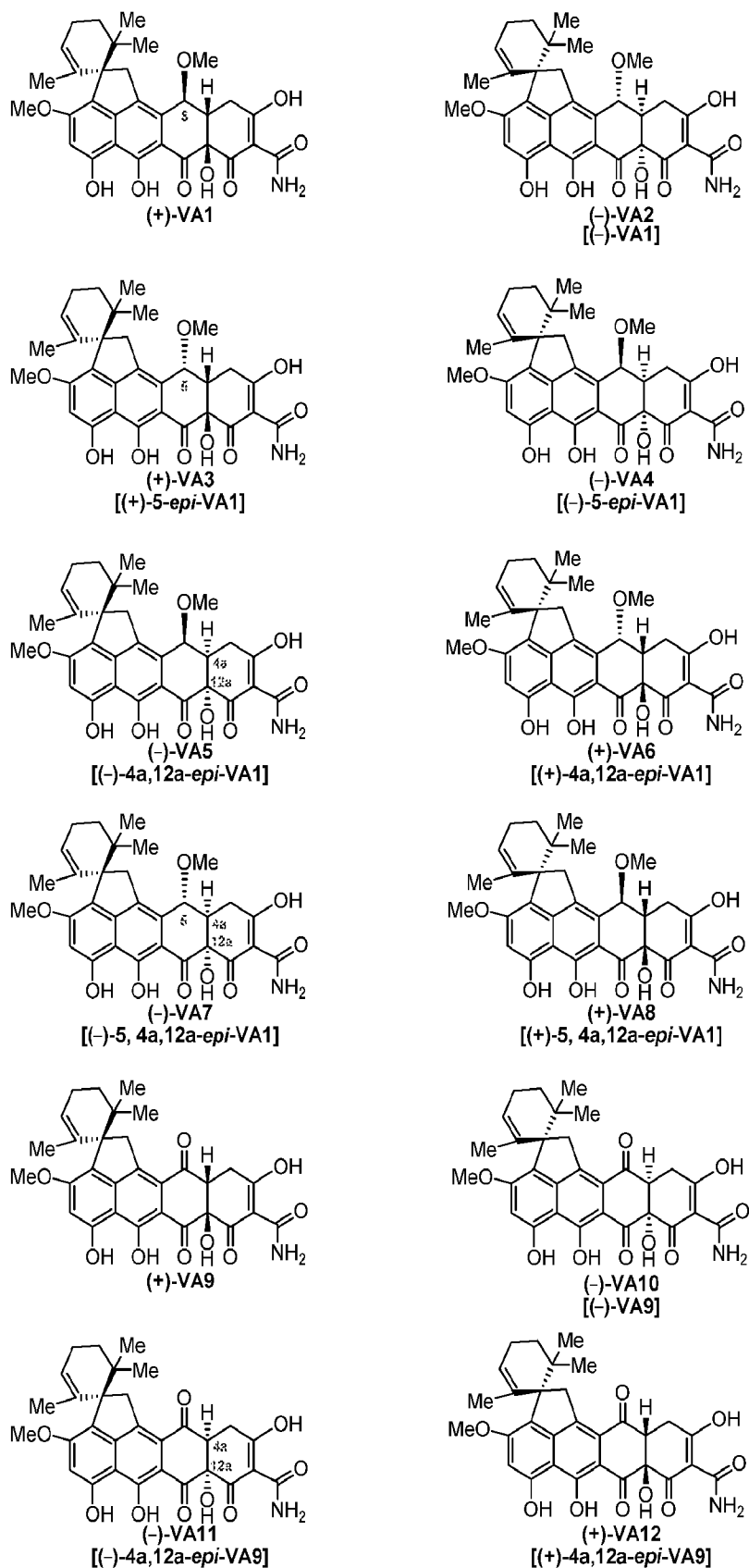
- ^aReagents and conditions: (a) **7** (6.02 g, 16.0 mmol scale), PTC17 (0.5 mol%), 40% aq. Cs₂CO₃, (CH₂)₂Cl₂, -30 °C, 10 days, 73%, 95:5 dr; (b) hexanes, 91%, >99:1 dr; (c) BF₃·Et₂O (0.05 equiv), CH₂Cl₂, -78 to 0 °C, 30 min, 74%, >99:1 er; (d) PIDA (1.2 equiv), MeOH:CH₂Cl₂ (1:1), 0 °C, 30 min, 25 °C, 30 min; (e) CSA (0.07 equiv), CH₂Cl₂, 0 °C, 5 min, 80% for two steps; (f) **10** (5.0 equiv), DMAP (10 equiv), Et₃N (30 equiv), CH₂Cl₂, 25 °C, 6 h, 95%. ^bNote: to avoid confusion, the numbering on (6*R*,17*S*)-**6**, (6*R*,15*S*)-**4** and (+)-**9** in this Scheme is based on the viridicatumtoxin numbering, as opposed to the carbon numbering of compound (10*R*,14*S*)-**6** (see Example 3), which is the same compound (6*S*,17*R*)-**6**, but numbered based on the anthrone numbering.

The total synthesis of (+)-viridicatumtoxin B [(+)-**1**] from key building block spiropentacycle (+)-**9** was successfully carried out through the same route and conditions (Similar to Scheme 6), and in similar yields, as those employed for its enantiomeric form [(-)-**1**] (see Scheme 7 and Example 3 for more details). The prepared viridicatumtoxin B exhibited the same sign of optical rotation as the one reported in the literature for the natural substrate {[α]_D²² = +118, *c* = 0.1, EtOH for synthetic (+)-**1**; [α]_D²⁵ = +18.3, *c* = 0.2, EtOH for natural (+)-**1** (Zheng *et al.*, 2008)}. The higher value for the synthetic material may simply reflect its higher purity, while the lower value reported for the natural substance may be due to lower purification and measurement difficulties due to its low natural abundance (Zheng *et al.*, 2008). However, the possibility of the latter occurring in nature in its scalemic form cannot be also excluded at this time.

D. Enantioselective Synthesis of Viridicatumtoxin B Analogues.

With a practical and enantioselective route to viridicatumtoxin B [(+)-**1**] and its antipode [(-)-**1**] and their precursors available to us, the construction of a number of their enantiopure analogues was carried out (see Scheme 8).

Scheme 8: Synthesized viridicatumtoxin B analogues (+)-VA1, (-)-VA2, (+)-VA3, (-)-VA4, (-)-VA5, (+)-VA6, (-)-VA7, (+)-VA8, (+)-VA9, (-)-VA10, (-)-VA11 and (+)-VA12.

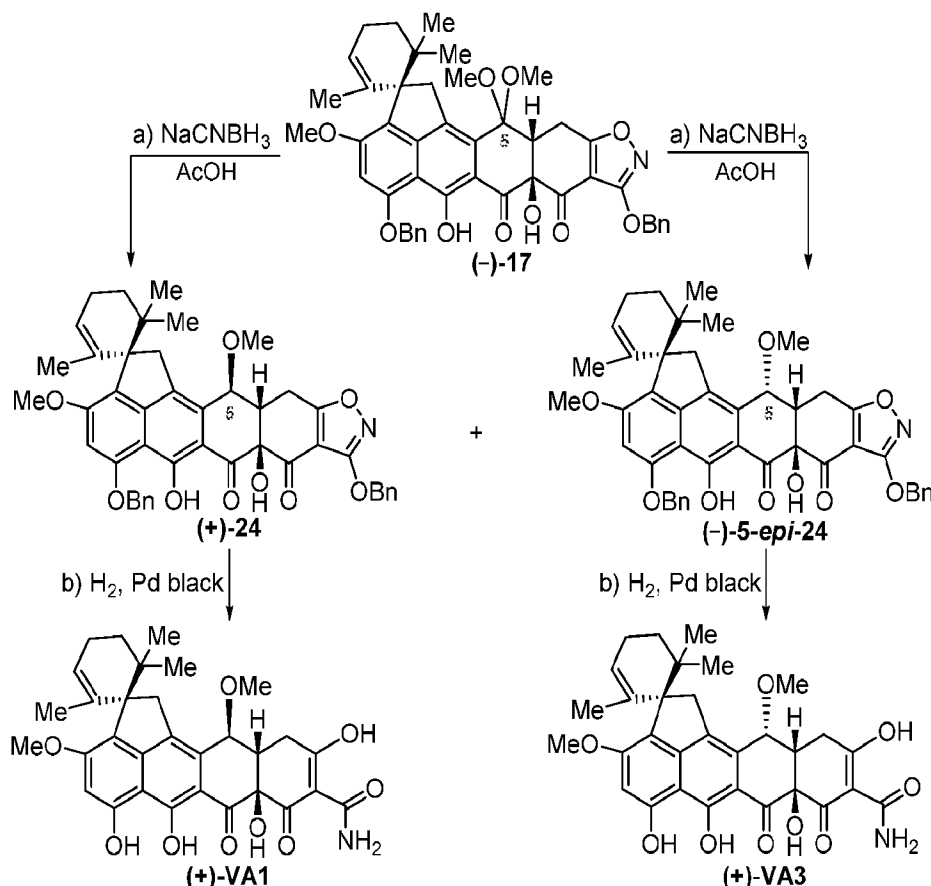


Of interest was comparing the antibacterial properties of the antipodal simpler viridicatumtoxin
 5 analogues shown in Scheme 8 such as (+)-VA1, (-)-VA2, (+)-VA3, (-)-VA4, (-)-VA5, (+)-VA6, (-)-VA7,

(+)-VA8, (+)-VA9, (-)-VA10, (-)-VA11 and (+)-VA12. Their synthesis proceeded smoothly from their required precursors, all of which were encountered in the earlier synthetic studies toward (+)- and (-)-viridicatumtoxin B as described above.

Scheme 9 summarizes the synthesis of (+)-VA1 and (+)-VA3 from precursor (-)-17. Thus, reduction of precursor (-)-17 with NaCNBH₃ in AcOH at ambient temperature resulted in the formation of a mixture of 5 β -methylether (+)-24 (48% yield) and its epimer 5 α -methylether (-)-5-*epi*-24 (32% yield), which were chromatographically separated. Hydrogenolysis of (+)-24 with Pd black as a catalyst then furnished viridicatumtoxin B analogue (+)-VA1 in 95% yield. Similar treatment of (-)-5-*epi*-24 led to analogue (+)-VA3 in comparable yield as for (+)-VA1 (see Scheme 9).

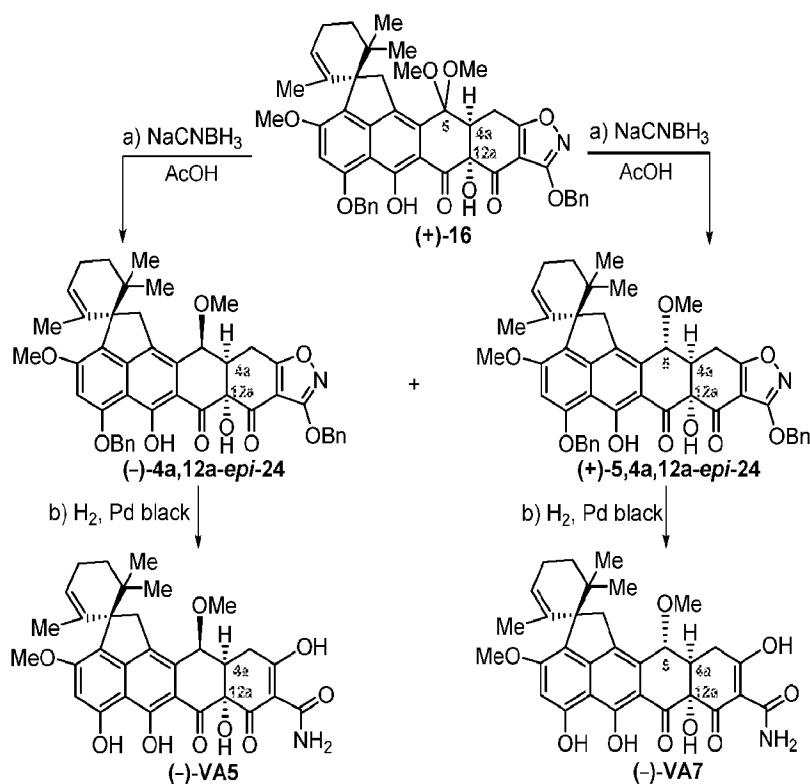
Scheme 9: Enantioselective Synthesis of Viridicatumtoxin B Analogues (+)-VA1 and (+)-VA3^a



^aReagents and conditions: (a) NaCNBH₃ (4.0 equiv), AcOH, 25 °C, 30 min, 48% for (+)-24, 32% for (-)-5-*epi*-24; (b) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%.

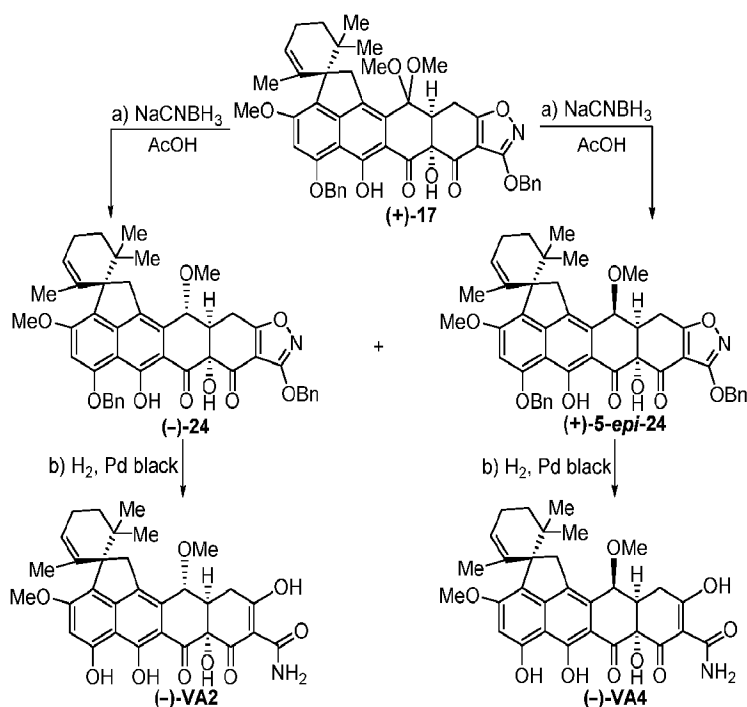
Analogues (-)-VA5 and (-)-VA7 were prepared from precursor (+)-16 in two steps, while the NaCNBH₃ reduction gave (-)-4a,12a-*epi*-24 in 17% yield and (+)-5,4a,12a-*epi*-24 in 51% yield, and the following hydrogenolysis of each produced analogues (-)-VA5 and (-)-VA7 in similar yields (see Scheme 10).

Scheme 10: Enantioselective Synthesis of Viridicatumtoxin B Analogues {(-)-VA5 [(-)-4a,12a-*epi*-VA1], (-)-VA7 [(-)-5,4a,12a-*epi*-VA1]}^a



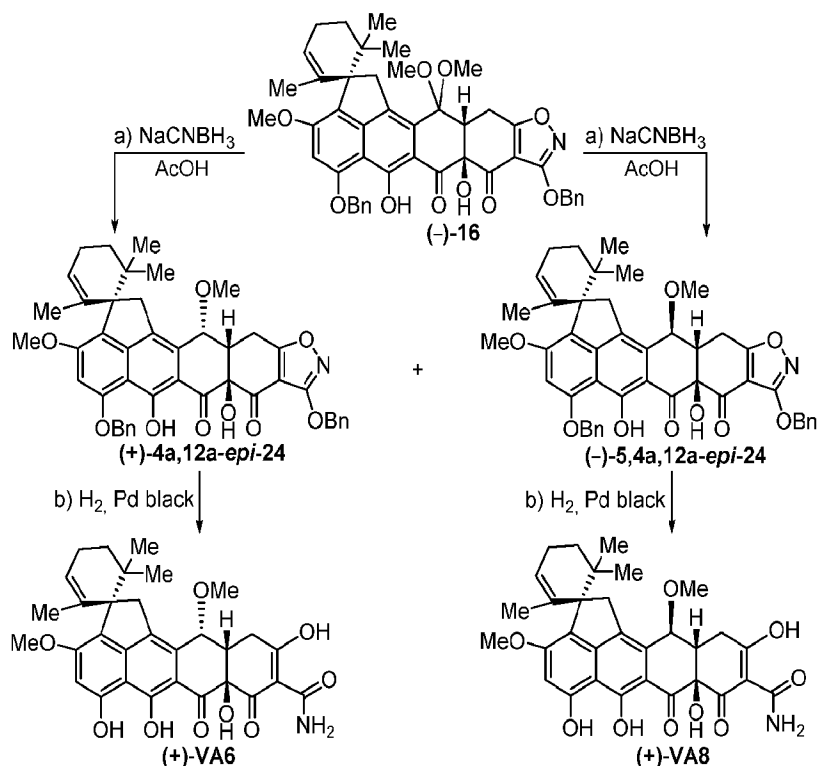
^aReagents and conditions: (a) NaCNBH₃ (4.0 equiv), AcOH, 25 °C, 30 min, 17% for **(-)-4a,12a-*epi*-24**, 51% for **(+)-5,4a,12a-*epi*-24**; (b) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%.

Analogues **(-)-VA2** and **(-)-VA4** were similarly prepared from their precursor **(+)-17** in comparable yields as for **(+)-VA1** and **(+)-VA3** as summarized in Scheme 11.

Scheme 11: Enantioselective Synthesis of Viridicatumtoxin B Analogues (–)-VA2 and (–)-VA4^a

^aReagents and conditions: (a) NaCNBH₃ (4.0 equiv), AcOH, 25 °C, 30 min, 45% for (–)-24, 30% for (+)-5-*epi*-24; (b) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%.

5 Analogues (+)-VA6 and (+)-VA8 were similarly prepared from their precursor (–)-16 in comparable yields as for (–)-VA5 and (–)-VA7 as summarized in Scheme 12.

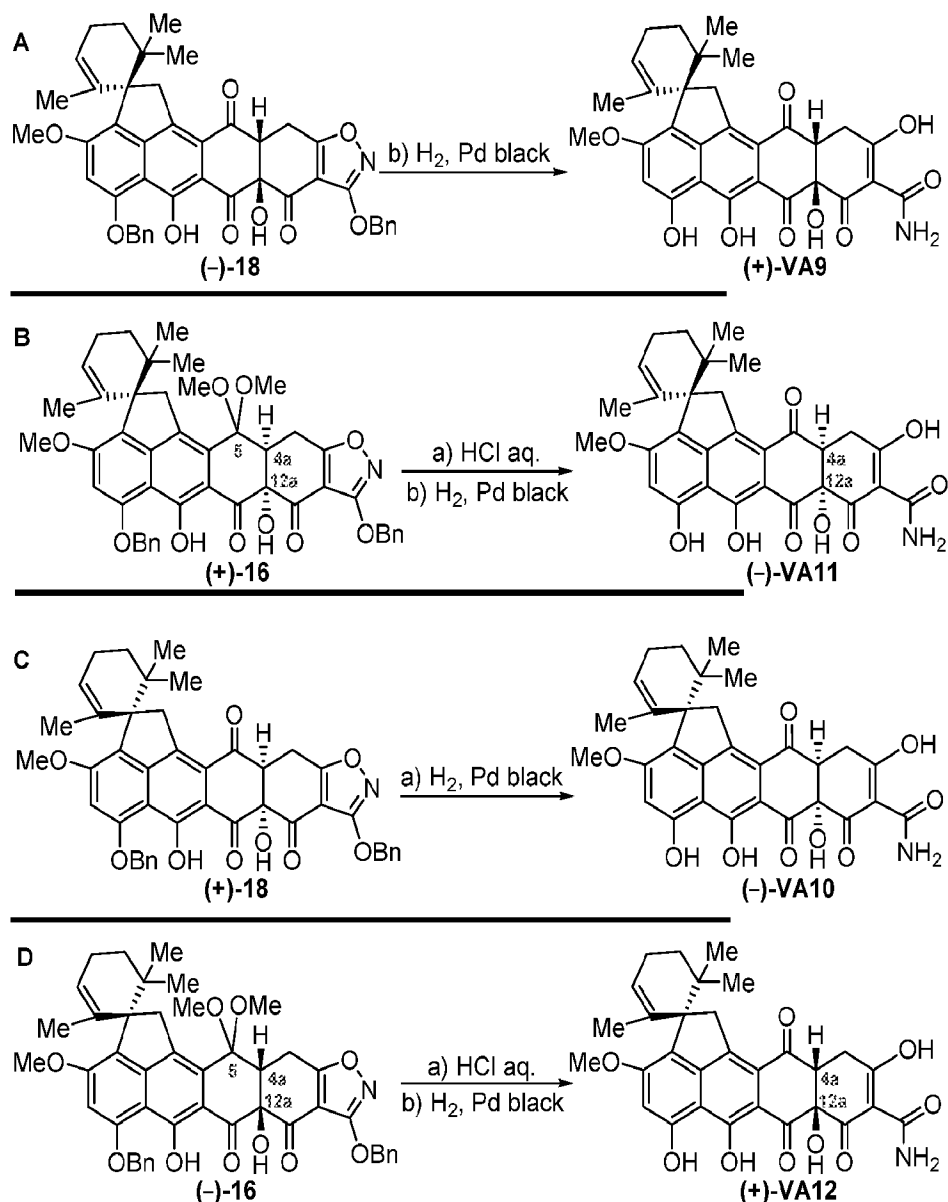
Scheme 12. Enantioselective Synthesis of Viridicatumtoxin B Analogues (+)-VA6 and (+)-VA8^a

^aReagents and conditions: (a) NaCNBH₃ (4.0 equiv), AcOH, 25 °C, 30 min, 16% for (+)-4a,12a-*epi*-24, 48% for (–)-5,4a,12a-*epi*-24; (b) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%.

10

Analogue (+)-**VA9** was obtained by hydrogenolysis of triketone (–)-**18** in 95% yield (Scheme 13, **A**). Analogue (–)-**VA11** was synthesized from hydrolysis of precursor (+)-**16** (quant. yield), followed by hydrogenolysis with Pd black (Scheme 13, **B**). Analogues (–)-**VA10** and (+)-**VA12** were similarly prepared from their respective precursors as summarized in Scheme 13 (**C** and **D**).

5 Scheme 13: Enantioselective Synthesis of Viridicatumtoxin B Analogues (+)-VA9, (–)-VA10, (–)-VA11 and (+)-VA12^a



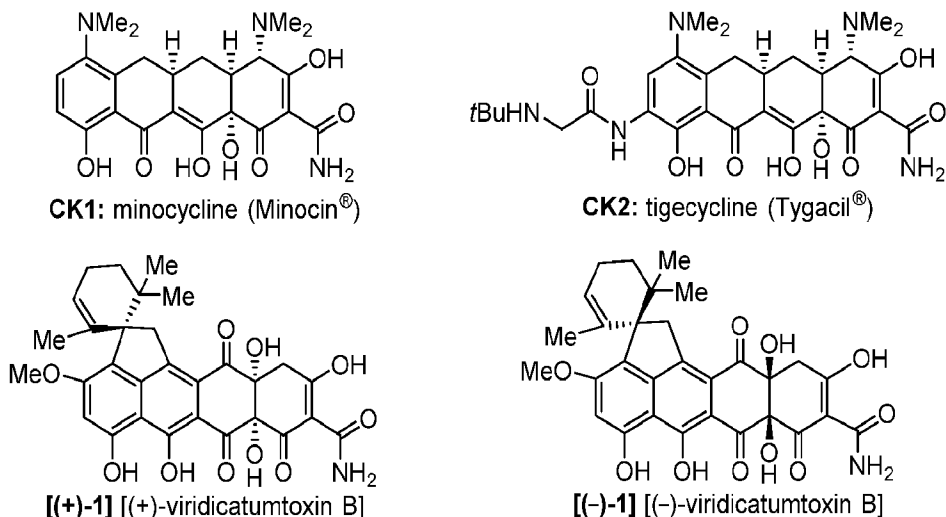
^aReagents and conditions: Panel A: (a) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%. Panel B: (a) 2 N aq. HCl, THF, 25 °C, 5 h, quant.; (b) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%. Panel C: (a) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%. Panel D: (a) 2 N aq. HCl, THF, 25 °C, 5 h, quant.; (b) H₂, Pd black (4.1 equiv), THF:MeOH 1:1, 25 °C, 10 min, 95%.

E. Biological Evaluation of Synthetic (+)- and (–)-Viridicatumtoxin B and Analogues.

The synthesized simpler enantiopure analogues (+)-**VA1**, (–)-**VA2**, (+)-**VA3**, (–)-**VA4**, (–)-**VA5**, (+)-**VA6**, (–)-**VA7**, (+)-**VA8**, (+)-**VA9**, (–)-**VA10**, (–)-**VA11** and (+)-**VA12** (see Figure 6 for structures), all lacking the C4a-hydroxyl group so cumbersome to install, together with (+)- and (–)-viridicatumtoxin B [(+)-**1** and (–)-**1**] were tested against a number of bacterial strains and compared to natural viridicatumtoxin B [(+)-**1**, reported

values¹ for *E. faecalis* KCTC5191, *E. faecium* KCTC3122, methicillin-resistant *Staphylococcus aureus* CCARM3167 (MRSA CCARM3167), *A. calcoaceticus* KCTC2357 and *E. coli* CCARM1356], minocycline (Minocin[®], CK1), and tigecycline (Tygacil[®], CK2) (see Scheme 13 for structures).

Scheme 13: Molecular structure of tetracycline drugs minocycline (CK1), tigecycline (CK2) (+) and (-)-viridicatumtoxin B [(+)-1 and (-)-1].



As shown in Table 5, the viridicatumtoxins and analogues tested exhibited antibacterial efficacy against Gram-positive bacteria [(*E. faecalis* S613, *E. faecium* 105, and methicillin-resistant *Staphylococcus aureus* 371 (MRSA 371)] but were less active against Gram-negative bacteria (i.e., *A. baumannii* AB210). Synthetic viridicatumtoxins B [(+)-1 and (-)-1] exhibited comparable antibacterial properties against these strains [*E. faecalis* S613, *E. faecium* 105, and MRSA 371: MIC = 2, 2, and 4 µg/mL, respectively, for (+)-1; MIC = 4, 4, and 8 µg/mL, respectively, for (-)-1] to those reported (Zheng *et al.*, 2008) for natural viridicatumtoxin B [(+)-1] against similar strains (*E. faecalis* KCTC5191, *E. faecium* KCTC3122, MRSA CCARM3167: MIC = 2, 0.5, and 0.5 µg/mL, respectively). Based on these data, it seems that synthetic (+)-viridicatumtoxin B [(+)-1] is twice as potent as its antipode (-)-viridicatumtoxin B [(-)-1]. It is known that MIC testing has a two-fold error, which makes the values for (+)-viridicatumtoxin B and (-)-viridicatumtoxin B within the error range for their MIC values. Regardless of this error, (+)-viridicatumtoxin B displayed high activity against the Gram-positive strains across the three independent replicates.

For the 5-methoxy analogues (+)-VA1, (-)-VA2, (+)-VA3, (-)-VA4, (-)-VA5, (+)-VA6, (-)-VA7 and (+)-VA8, the potency against the tested strains were generally lower than those of synthetic viridicatumtoxin B [(+)-1], except for analogue (+)-VA6, which exhibited comparable potencies against *E. faecalis* S613 (MIC = 1 µg/mL) and *E. faecium* 105 (MIC = 2 µg/mL). However, all four 5,12-diketo analogues [(+)-VA9, (-)-VA10, (-)-VA11 and (+)-VA12] demonstrated stronger antibacterial properties than synthetic viridicatumtoxin B [(+)-1] against *E. faecalis* S613 [(+)-VA9: MIC = 0.5 µg/mL; (-)-VA10: MIC = 1 µg/mL, (-)-VA11: MIC = 1 µg/mL; (+)-VA12: MIC = 1 µg/mL], *E. faecium* 105 [(+)-VA9: MIC = 2 µg/mL; (-)-VA10: MIC = 1 µg/mL, (-)-VA11: MIC = 0.5 µg/mL; (+)-VA12: MIC = 1 µg/mL] and MRSA 371 [(+)-VA9: MIC = 2 µg/mL; (-)-VA10: MIC = 2 µg/mL, (-)-VA11: MIC = 2 µg/mL; (+)-VA12: MIC = 2 µg/mL] (see Table 5). Without wishing to be bound by any theory, it is believed that these results provide two considerations: first, the C-4a

hydroxy group is not critical for activity, and finally, the stereochemical orientation of the molecule is generally unimportant to the activity of the molecule.

The modified synthetic route resulted in enantiopure viridicatumtoxin B with an 0.985% overall yield from key building block **7** as compared to 0.267% yield for the original route to racemic viridicatumtoxin B from the same prochiral intermediate (**7**). This new methods resulted in a 3.7-fold improved efficiency. Furthermore, these studies revealed a biologically superior and molecularly simpler potential drug candidate [(-)-**VA10**] than viridicatumtoxin B. This analogue may be prepared from precursor **32** in one step and 95% yield as opposed to the natural product that requires six steps for its generation from the same intermediate and in 11% overall yield. These improvements bode well for compound (-)-**VA10** and its siblings compounds, (+)-**VA9**, (-)-**VA11** and (+)-**VA12**, as potential drug candidates for further development. Despite the literature reported activity of viridicatumtoxin B against several Gram-negative bacterial strains (Zheng *et al.*, 2008), the tested compounds proved inactive against *A. baumannii* AB210.

Table 5. Minimum Inhibitory Concentration (MIC) Data of Compounds Against Gram-positive and Gram-negative Bacteria and Comparison with Selected Literature Data

Entry	Gram-(+)						Gram-(-)		
	This study ^a			Reference (Zheng <i>et al.</i> , 2008)			This study ^a	Reference (Zheng <i>et al.</i> , 2008)	Gram-(-)
	<i>E. faecalis</i> S613	<i>E. faecium</i> 105	MRSA 371	<i>E. faecalis</i> KCTC5191 ^b	<i>E. faecium</i> KCTC3122 ^b	MRSA CCARM3167 ^b			
CK1	8	8	1	—	—	—	4	—	—
CK2	0.5	0.25	2	—	—	—	0.5	—	—
(+)-1	2	2	4	2 ^c	0.5 ^c	0.5 ^c	64	1 ^c	>64 ^c
(-)-1	4	4	8	—	—	—	64	—	—
(+)-VA1	8	8	8	—	—	—	64	—	—
(-)-VA2	16	16	32	—	—	—	64	—	—
(+)-VA3	16	16	8	—	—	—	64	—	—
(-)-VA4	8	16	64	—	—	—	64	—	—
(-)-VA5	128	64	>128	—	—	—	64	—	—
{+}-VA6	1	2	64	—	—	—	64	—	—
(-)-VA7	4	8	8	—	—	—	64	—	—
(+)-VA8	2	8	8	—	—	—	64	—	—
{+}-VA9	0.5	2	2	—	—	—	64	—	—
{-}-VA10	1	1	2	—	—	—	64	—	—
{-}-VA11	1	0.5	2	—	—	—	64	—	—
{+}-VA12	1	1	2	—	—	—	64	—	—

^aMIC assays were run in triplicate; data are given in units of µg/mL; ^bTaken from reference (Zheng *et al.*, 2008) for comparison; ^cEnantiopure material [(+)-1] isolated from *Penicillium* sp. FR11 was used in reference (Zheng *et al.*, 2008).

EXAMPLE 2 – General Methods and Materials

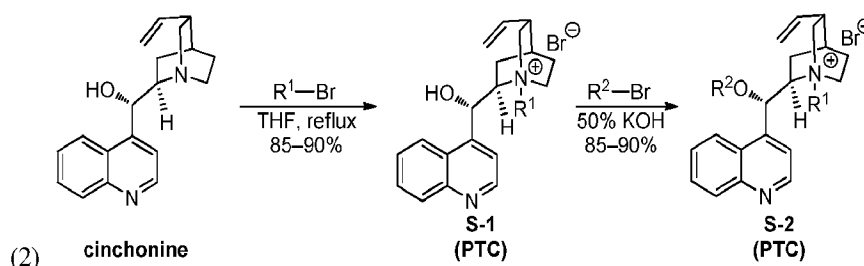
All reactions were carried out under an argon atmosphere unless otherwise noted. Methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), toluene, methanol (MeOH), dimethylformamide (DMF), diisopropylethylamine, and triethylamine were dried prior to use by passage through an activated alumina column unless otherwise noted (Pangborn, *et al.*, 1996). Anhydrous 1,2-dichloroethane [$(\text{CH}_2)_2\text{Cl}_2$], ethyl acetate, chloroform (CHCl_3) and tetrachloromethane (CCl_4) were purchased from commercial suppliers and stored under argon. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^1H NMR) homogenous material, unless otherwise stated.

Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) and were visualized using UV light and an ethanolic solution of phosphomolybdic acid and cerium sulfate or an aqueous solution of potassium permanganate. Flash column chromatography using E. Merck silica gel (60, particle size 0.040–0.063 mm) was performed as described by Still (Still, *et al.*, 1978). NMR spectra were recorded on a Bruker DRX-600 equipped with a 5 mm DCH cryoprobe, a Bruker 500 UltraShield or a Varian Mercury-300BB spectrometer and referenced using the residual undeuterated solvent signal for ^1H NMR [$\delta_{\text{H}} = 7.26$ (CDCl_3), 5.32 (CD_2Cl_2), 7.16 (C_6D_6), 2.05 (acetone- d_6), 2.50 (DMSO- d_6), and 3.31 (CD_3OD) ppm] and ^{13}C deuterated solvent signal for ^{13}C NMR [$\delta_{\text{C}} = 77.16$ (CDCl_3), 53.84 (CD_2Cl_2), 128.06 (C_6D_6), 29.84 (acetone- d_6), 39.50 (DMSO- d_6), and 49.00 (CD_3OD) ppm], or using an external reference for ^{19}F NMR [$\delta_{\text{F}} = 0$ (CCl_3F) ppm]. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, ap = apparent.

ATR-Infrared (IR) spectra were recorded on a Perkin-Elmer 100 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD/TOF mass spectrometer using ESI (electrospray ionization) or CI (Chemical ionization); or a Shimadzu Ion Trap-TOF using ESI. Optical rotations were recorded on a POLARTRONIC M100 polarimeter at 589 nm, and are reported in units of 10^{-1} ($\text{deg cm}^2 \text{g}^{-1}$). Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus or a Thomas Hoover uni-melt capillary melting point apparatus. Crystallizations were carried out from the solvents given in parentheses after the melting points. X-Ray crystallographic analysis data were collected using a Bruker Smart-APEX instrument (CCD detector) or a Bruker Kappa APEX-II instrument (CCD detector). HPLC analyses and purifications were performed on a Shimadzu LC system with UV/VIS detector using chiralcel columns or an Atlantis prep T3 OBD column.

EXAMPLE 3 – Compound Characterization

(1) Phase Transfer Catalyst (PTC) Synthesis

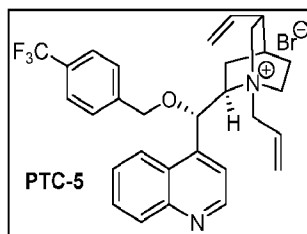


General procedure for the PTC synthesis: The PTCs were synthesized according to as described in the literature (Corey and Bo, 1997; Lian *et al.*, 2010).

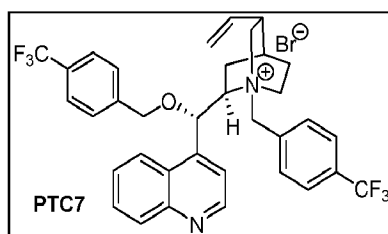
Procedure A: To a stirred suspension of cinchonine (589 mg, 2.00 mmol, 1.0 equiv) in THF (20 mL) was added desired bromide derivative (R^1 -Br, 2.00 mmol, 1.0 equiv), and the mixture was refluxed at 80 °C for 3 h, then cooled to 25 °C and poured into Et₂O (80 mL). The solid was filtered off and recrystallized from MeOH/Et₂O to obtain product **S-1** as a crystalline solid.

Procedure B: To a stirred suspension of **S-1** (2.00 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) was added bromide derivative (R^2 -Br, 6.00 mmol, 3.0 equiv) and 50% aq. KOH (1.00 mL, 10.0 mmol, 10 equiv). The resulting mixture was stirred vigorously at 25 °C for 4 h. The mixture was diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Recrystallization of the residue from MeOH/Et₂O afforded product **S-2** as a slightly yellow solid.

PTC1 (Corey *et al.*, 1998), **PTC2** (Kitamura *et al.*, 2005), **PTC18** (Ooi *et al.*, 2003), **PTC19** (Park *et al.*, 2002), **PTC20** (Shen *et al.*, 2006) and **PTC21** ((Rubina *et al.*, 1987) were purchased from Acros, J & K Chemicals, Inc., Sigma-Aldrich, and TCI. All other catalysts were synthesized following the above described procedures. Previously reported catalysts were characterized by comparing their literature physical data (**PTC3** (Iwabuchi *et al.*, 1999), **PTC4** (Lee and Wong, 1991), **PTC6** (Kobbelgaard *et al.*, 2014; Liang *et al.*, 2014), **PTC8** (Scott *et al.*, 2008), **PTC14** (Zeng *et al.*, 2013; Adam *et al.*, 2002; Xie *et al.*, 2014), **PTC16** (Johnston *et al.*, 2015; Li *et al.*, 2013), **PTC22** (Moss *et al.*, 2008), **PTC24** (Zhang *et al.*, 2009), **PTC25** (Zhang *et al.*, 2009), **PTC26** (Díez-Barra *et al.*, 1998), **PTC27** (Lee and Wong, 1991), **PTC28** (Lee and Wong, 1991), **PTC29** (Scott *et al.*, 2008), **PTC32** (Arai *et al.*, 1998), **PTC33** (Arai *et al.*, 1999), **PTC34** (Li *et al.*, 2013), **PTC35** (Borszky *et al.*, 1999), **PTC36** (Borszky *et al.*, 1999), **PTC37** (Jew *et al.*, 2002), **PTC39** (Belyk *et al.*, 2010), and **PTC40** (Belyk *et al.*, 2010)).

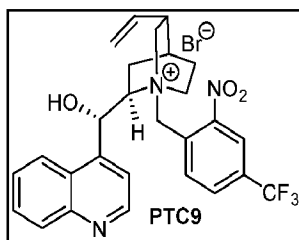


(3ξ,9S)-1-Allyl-9-[[4-(trifluoromethyl)benzyl]oxy]cinchonan-1-ium bromide (PTC5): According to general procedures **A** and **B**, cinchonine (589 mg, 2.00 mmol, 1.0 equiv) was reacted with allyl bromide (173 μL, 242 mg, 2.00 mmol, 1.0 equiv), followed by 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.43 g, 6.00 mmol, 3.0 equiv) to give product **PTC5** (928 mg, 1.60 mmol, 80% yield for two steps) as a slightly yellow solid. **PTC5**: $R_f=0.50$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +73.3$ ($c=1.0$, CH_2Cl_2); m.p. = 139–141 °C (MeOH/Et₂O); FT-IR (film) ν_{max} : 3410, 3076, 2953, 2882, 1640, 1619, 1590, 1570, 1533, 1509, 1461, 1421, 1400, 1323, 1272, 1235, 1211, 1163, 1121, 1113, 1065, 1018, 997, 950, 925, 872, 850, 826, 800, 779, 760, 722, 679, 668 cm^{-1} ; ^1H NMR: (CDCl_3 , 600 MHz) δ 8.96 (d, $J=3.6$ Hz, 1 H), 8.59 (d, $J=7.4$ Hz, 1 H), 8.14 (d, $J=8.2$ Hz, 1 H), 7.86 (s, 1 H), 7.78 (ap t, $J=7.1$ Hz, 1 H), 7.67 (d, $J=7.6$ Hz, 2 H), 7.57 (d, $J=7.8$ Hz, 1 H), 7.50 (d, $J=7.6$ Hz, 2 H), 6.24–6.15 (m, 2 H), 5.92–5.75 (m, 2 H), 5.71 (d, $J=9.9$ Hz, 1 H), 5.41 (s, 1 H), 5.22 (d, $J=10.4$ Hz, 1 H), 5.08 (d, $J=17.2$ Hz, 1 H), 4.75 (b, 1 H), 4.72 (d, $J=11.7$ Hz, 1 H), 4.62 (ap t, $J=10.6$ Hz, 1 H), 4.19 (s, 1 H), 4.05 (s, 1 H), 4.03–3.95 (m, 1 H), 3.74 (t, $J=10.7$ Hz, 1 H), 3.62 (s, 1 H), 2.76 (d, $J=7.4$ Hz, 1 H), 2.36 (s, 1 H), 1.98 (s, 1 H), 1.95 (d, $J=12.2$ Hz, 1 H), 1.82 (d, $J=9.0$ Hz, 1 H), 1.09 (s, 1 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 149.6, 148.7, 139.8, 139.5, 135.4, 131.3 (q, $J=32.7$ Hz), 130.5 (b), 130.4 (b), 129.5, 129.3 (b), 128.6, 128.3, 126.1 (q, $J=3.4$ Hz), 125.2, 124.2, 123.9 (q, $J=272.1$ Hz), 118.9 (b), 118.1, 74.2 (b), 70.8, 65.9 (b), 61.7, 56.6, 56.0, 37.6, 27.0, 23.6, 21.9 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ –61.8 (s) ppm; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{32}\text{F}_3\text{N}_2\text{O}^+ [M-\text{Br}]^+$ 493.2461, found 493.2462.



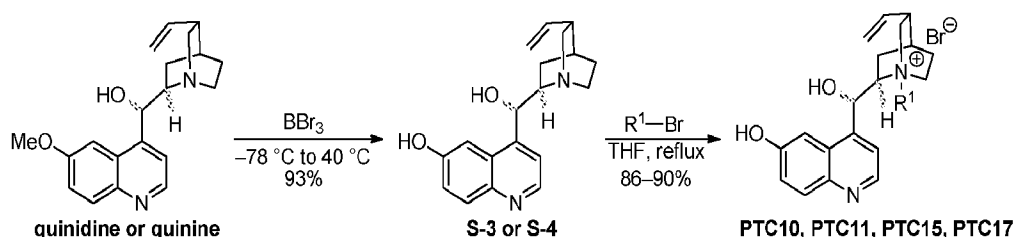
(3ξ,9S)-1-[4-(Trifluoromethyl)benzyl]-9-[[4-(trifluoromethyl)benzyl]oxy]cinchonan-1-ium bromide (PTC7): According to general procedures **A** and **B**, cinchonine (589 mg, 2.0 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-(trifluoromethyl)benzene (478 mg, 2.00 mmol, 1.0 equiv), followed by 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.43 g, 6.00 mmol, 3.0 equiv) to give product **PTC7** (1.12 g, 1.58 mmol, 79% yield for two steps) as a slightly yellow solid. **PTC7**: $R_f=0.60$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +79.2$ ($c=1.0$, CH_2Cl_2); m.p. = 157–159 °C (MeOH/Et₂O); FT-IR (film) ν_{max} : 3396, 2950, 1639, 1620, 1590, 1571, 1509, 1461, 1423, 1405, 1375, 1323, 1235, 1212, 1164, 1117, 1066, 1036, 1018, 933, 865, 852, 832, 799, 779, 760, 710, 682, 654 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.98 (d, $J=4.4$ Hz, 1 H), 8.94 (bs, 1 H), 8.10 (d, $J=8.5$ Hz, 1 H), 7.92–7.79 (m, 3 H), 7.77–7.68 (m, 3 H), 7.72 (d, $J=7.4$ Hz, 2 H), 7.68–7.54 (m, 5 H), 6.61 (d, $J=11.8$ Hz, 1 H), 6.38 (s, 1 H), 5.95–5.70 (m, 1 H), 5.44 (s, 1 H), 5.27 (d, $J=10.4$ Hz, 1 H), 5.09

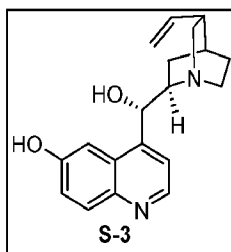
(d, $J=17.2$ Hz, 1 H), 4.87 (d, $J=11.9$ Hz, 1 H), 4.70 (d, $J=11.8$ Hz, 1 H), 4.32 (d, $J=10.2$ Hz, 1 H), 4.09–4.08 (m, 1 H), 3.41–3.22 (m, 1 H), 2.74 (ap q, $J=10.1$, 9.5 Hz, 1 H), 2.44 (ap q, $J=8.8$ Hz, 1 H), 2.36 (bs, 1 H), 1.97 (s, 1 H), 1.94–1.86 (m, 1 H), 1.82–1.73 (m, 1 H), 1.13 (s, 1 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 149.4, 148.6, 140.1, 139.3, 135.1, 134.6, 132.60 (q, $J=32.8$ Hz), 131.31 (q, $J=32.9$ Hz), 131.0, 130.5 (b), 130.0 (b), 129.3 (b), 128.8, 128.5, 126.25 (q, $J=3.7$ Hz), 125.98 (q, $J=3.8$ Hz), 125.1, 123.8 (q, $J=272.1$ Hz), 123.5 (q, $J=272.8$ Hz), 118.8 (b), 118.3, 74.8 (b), 71.1, 66.2 (b), 60.8, 56.0, 54.7, 37.6, 27.0, 23.4, 22.1 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -61.8 (s), -62.1 (s) ppm; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{33}\text{F}_6\text{N}_2\text{O}^+ [\text{M}-\text{Br}]^+$ 611.2492, found 611.2483.



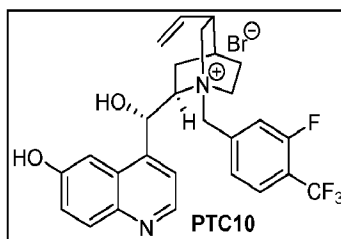
(3*S*,9*S*)-9-Hydroxy-1-[2-nitro-4-(trifluoromethyl)benzyl]cinchonan-1-ium bromide (PTC9):

According to general procedure A, cinchonine (589 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-2-nitro-4-(trifluoromethyl)benzene (568 mg, 2.00 mmol, 1.0 equiv) to give product **PTC9** (1.04 g, 1.80 mmol, 90% yield) as a white solid. **PTC9**: $R_f=0.30$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=+235.2$ ($c=1.0$, MeOH); m.p.=210–212 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3386, 3212, 2955, 2891, 1631, 1591, 1575, 1543, 1508, 1462, 1415, 1348, 1327, 1292, 1236, 1211, 1183, 1162, 1134, 1093, 1042, 1028, 1003, 933, 901, 862, 829, 814, 797, 777, 764, 714, 691, 655 cm^{-1} ; ^1H NMR (600 MHz, DMSO- d_6) δ 8.99 (d, $J=4.4$ Hz, 1 H), 8.61 (s, 1 H), 8.45 (ap t, $J=8.6$ Hz, 2 H), 8.39 (dd, $J=7.2$, 1.3 Hz, 1 H), 8.11 (d, $J=8.3$ Hz, 1 H), 7.85 (ddd, $J=8.3$, 7.0, 1.0 Hz, 1 H), 7.82 (d, $J=4.4$ Hz, 1 H), 7.75 (ddd, $J=8.1$, 6.9, 1.2 Hz, 1 H), 6.93 (d, $J=2.2$ Hz, 1 H), 6.52 (s, 1 H), 6.06–5.90 (m, 1 H), 5.69 (d, $J=13.1$ Hz, 1 H), 5.62–5.45 (m, 1 H), 5.23 (d, $J=10.4$ Hz, 1 H), 5.15 (d, $J=17.3$ Hz, 1 H), 4.22–4.10 (m, 2 H), 4.08 (ap t, $J=9.4$ Hz, 1 H), 3.33–3.14 (m, 2 H), 2.59 (dd, $J=16.9$, 8.3 Hz, 1 H), 2.33–2.19 (m, 1 H), 1.87 (s, 1 H), 1.84–1.77 (m, 1 H), 1.75–1.72 (m, 1 H), 1.11–0.95 (m, 1 H) ppm; ^{13}C NMR (151 MHz, DMSO- d_6) δ 151.5, 150.2, 147.6, 144.8, 138.2, 136.9, 131.8 (q, $J=33.9$ Hz), 130.1 (q, $J=4.1$ Hz), 129.8, 129.4, 127.2, 126.0, 124.4, 123.9, 123.2 (q, $J=4.0$ Hz), 122.8 (q, $J=272.9$ Hz), 120.0, 117.0, 67.6, 65.2, 56.3, 56.0, 54.8, 36.9, 25.9, 23.1, 20.7 ppm; ^{19}F NMR (282 MHz, DMSO- d_6) δ -60.7 (s) ppm; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_3^+ [\text{M}-\text{Br}]^+$ 498.1999, found 498.2000.

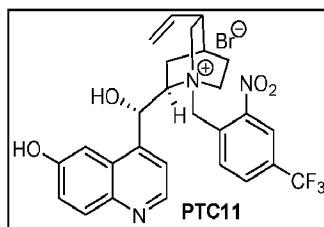




(3ξ,9S)-Cinchonan-6',9-diol (S-3): Catalyst precursor **S-3** was prepared following a similar procedure as above starting from quinidine (Shi *et al.*, 2007). To a stirred solution of quinidine (3.25 g, 10.0 mmol, 1.0 equiv) in CH₂Cl₂ (200 mL) flushed with argon was added a solution of BBr₃ (3.78 mL, 40.0 mmol, 4.0 equiv) in CH₂Cl₂ (30 mL) dropwise at −78 °C. The reaction mixture was allowed to warm to 25 °C and then refluxed at 40 °C for 2 h. Then, the reaction was quenched by addition of 40% aq. NH₄OH solution (100 mL) at 0 °C, followed by addition of H₂O (100 mL) and CH₂Cl₂ (100 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL), the combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, EtOAc:Et₃N:MeOH, 50:1:2) to give precursor **S-3** (2.89 g, 9.31 mmol, 93% yield) as a yellow solid. The spectral data of this compound matched those reported in the literature (Li *et al.*, 2004).

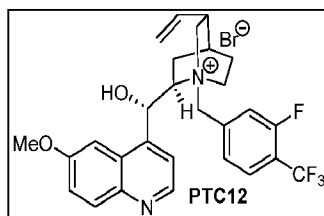


(3ξ,9S)-1-[3-Fluoro-4-(trifluoromethyl)benzyl]-6',9-dihydroxy-cinchonan-1-ium bromide (PTC10): According to general procedure A, catalyst precursor **S-3** (621 mg, 2.00 mmol, 1.0 equiv) was treated with 4-(bromomethyl)-2-fluoro-1-(trifluoromethyl)benzene (514 mg, 2.00 mmol, 1.0 equiv) to give product **PTC10** (978 mg, 1.74 mmol, 87% yield) as a white solid. **PTC10**: R_f=0.20 (silica gel, 10% MeOH in CH₂Cl₂); [α]_D²² = +180.5 (c=1.0, MeOH); m.p. = 216–218 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max}: 3172, 2890, 2815, 1621, 1587, 1531, 1513, 1466, 1438, 1404, 1326, 1293, 1254, 1239, 1219, 1180, 1135, 1081, 1044, 1027, 1006, 927, 854, 790, 773, 760, 735, 695, 680 cm^{−1}; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.05 (s, 1 H), 8.74 (d, *J*=4.4 Hz, 1 H), 8.13 (d, *J*=11.4 Hz, 1 H), 8.01 (ap t, *J*=7.8 Hz, 1 H), 7.95–7.92 (m, 2 H), 7.76 (d, *J*=2.2 Hz, 1 H), 7.68 (d, *J*=4.4 Hz, 1 H), 7.35 (dd, *J*=9.0, 2.3 Hz, 1 H), 6.75 (d, *J*=4.0 Hz, 1 H), 6.31 (s, 1 H), 6.05–5.94 (m, 1 H), 5.37 (d, *J*=12.3 Hz, 1 H), 5.24 (s, 1 H), 5.22 (d, *J*=6.8 Hz, 1 H), 5.13 (d, *J*=12.3 Hz, 1 H), 4.25 (ddd, *J*=11.5, 8.5, 2.3 Hz, 1 H), 4.08 (ap t, *J*=10.7 Hz, 1 H), 3.96 (ap t, *J*=9.4 Hz, 1 H), 3.54 (ap t, *J*=11.3 Hz, 1 H), 3.14–3.06 (m, 1 H), 2.70–2.52 (m, 1 H), 2.36–2.21 (m, 1 H), 1.89 (s, 1 H), 1.82–1.72 (m, 2 H), 1.12–1.06 (m, 1 H) ppm; ¹³C NMR (151 MHz, DMSO-*d*₆) δ 158.59 (d, *J*=254.4 Hz), 156.0, 146.7, 142.9, 142.6, 137.1, δ 135.57 (d, *J*=8.2 Hz), 131.4, 130.74 (d, *J*=3.6 Hz), 127.76 (q, *J*=4.5 Hz), 125.5, 122.50 (q, *J*=272.2 Hz), 122.46 (d, *J*=21.2 Hz), 121.8, 119.8, 118.02 (qd, *J*=32.6, 11.9 Hz), 117.1, 104.7, 67.5, 64.8, 60.5, 56.2, 54.2, 36.8, 26.2, 23.1, 20.6 ppm; ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ −59.24 (d, *J*=12.3 Hz, 3 F, CF₃), −114.1–−114.0 (m, 1 F, C_{ar}F) ppm; HRMS (ESI) calcd for C₂₇H₂₇F₄N₂O₂⁺ [*M*–Br]⁺ 487.2003, found 487.2002.



(3ξ,9S)-6',9-Dihydroxy-1-[2-nitro-4-(trifluoromethyl)benzyl]cinchonan-1-ium bromide (PTC11):

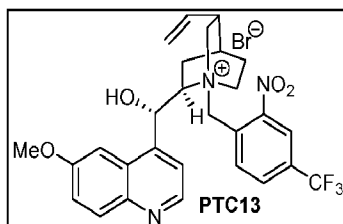
According to general procedure A, catalyst intermediate **S-3** (621 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-2-nitro-4-(trifluoromethyl)benzene (568 mg, 2.00 mmol, 1.0 equiv) to give product **PTC11** (967 mg, 1.72 mmol, 86% yield) as a pale yellow solid. **PTC11**: $R_f=0.25$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=+236.8$ ($c=1.0$, MeOH); m.p.=200–202 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3205, 2959, 1621, 1594, 1577, 1543, 1508, 1465, 1396, 1349, 1327, 1291, 1270, 1237, 1221, 1184, 1161, 1138, 1094, 1043, 1004, 929, 901, 861, 832, 782, 760, 730, 714, 693 cm^{-1} ; ^1H NMR (600 MHz, DMSO- d_6) δ 9.96 (s, 1H), 8.74 (d, $J=4.4$ Hz, 1H), 8.61 (s, 1H), 8.51 (d, $J=8.1$ Hz, 1H), 8.39 (d, $J=7.0$ Hz, 1H), 7.95 (d, $J=9.0$ Hz, 1H), 7.81 (d, $J=2.3$ Hz, 1H), 7.68 (d, $J=4.4$ Hz, 1H), 7.38 (dd, $J=9.1$, 2.4 Hz, 1H), 6.86 (d, $J=2.2$ Hz, 1H), 6.32 (s, 1H), 6.08–5.90 (m, 1H), 5.74 (d, $J=13.4$ Hz, 1H), 5.59 (d, $J=13.0$ Hz, 1H), 5.22 (d, $J=10.4$ Hz, 1H), 5.14 (d, $J=17.3$ Hz, 1H), 4.17 (ap t, $J=9.8$ Hz, 2H), 4.08 (ap t, $J=9.5$ Hz, 1H), 3.32–3.22 (m, 2H), 2.58 (dd, $J=16.8$, 8.2 Hz, 1H), 2.35–2.14 (m, 1H), 1.91–1.70 (m, 3H), 1.14–0.97 (m, 1H) ppm; ^{13}C NMR (151 MHz, DMSO- d_6) δ 156.0, 151.6, 146.7, 142.9, 142.5, 138.3, 136.9, 131.9 (q, $J=33.5$ Hz), 131.3, 130.1 (q, $J=2.9$ Hz), 126.0, 125.6, 123.3 (q, $J=3.4$ Hz), 122.8 (q, $J=273.6$ Hz), 121.8, 119.8, 117.1, 104.8, 67.4, 65.4, 56.22, 56.17, 54.8, 37.0, 25.9, 23.2, 20.7 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ –62.4 (s) ppm; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_4^+$ $[M-\text{Br}]^+$ 514.1948, found 514.1945.



(3ξ,9S)-1-[3-Fluoro-4-(trifluoromethyl)benzyl]-9-hydroxy-6'-methoxycinchonan-1-ium bromide

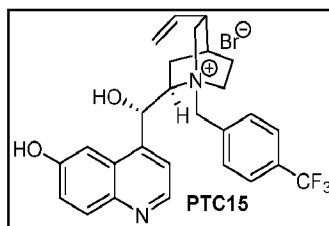
(PTC12): According to general procedure A, quinidine (649 mg, 2.00 mmol, 1.0 equiv) was treated with 4-(bromomethyl)-2-fluoro-1-(trifluoromethyl)benzene (514 mg, 2.00 mmol, 1.0 equiv) to give product **PTC12** (1.06 g, 1.82 mmol, 91% yield) as a white solid. **PTC12**: $R_f=0.30$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=+160.2$ ($c=1.0$, CH_2Cl_2); m.p.=182–184 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3225, 2946, 2832, 1622, 1588, 1509, 1473, 1460, 1437, 1394, 1357, 1324, 1296, 1255, 1241, 1227, 1208, 1179, 1131, 1093, 1049, 1025, 1007, 958, 932, 916, 899, 850, 828, 774, 760, 739, 718, 693, 679 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.48 (d, $J=4.2$ Hz, 1H), 7.84 (d, $J=10.3$ Hz, 1H), 7.77 (d, $J=9.2$ Hz, 1H), 7.70 (d, $J=7.8$ Hz, 1H), 7.67 (d, $J=4.3$ Hz, 1H), 7.50–7.48 (m, 2H), 7.05 (dd, $J=9.1$, 2.1 Hz, 1H), 6.55 (d, $J=5.2$ Hz, 1H), 6.38 (s, 1H), 5.85 (ddd, $J=17.4$, 10.4, 7.1 Hz, 1H), 5.76 (d, $J=12.0$ Hz, 1H), 5.69 (d, $J=12.0$ Hz, 1H), 5.22–5.17 (m, 2H), 4.53 (ap t, $J=10.0$ Hz, 2H), 4.18–4.07 (m, 1H), 3.79 (s, 3H), 3.24 (ap t, $J=11.4$ Hz, 1H), 2.77 (dd, $J=20.5$, 9.9 Hz,

1 H), 2.38 (dd, $J=16.8, 8.5$ Hz, 1 H), 2.35–2.27 (m, 1 H), 1.81 (s, 1 H), 1.72–1.63 (m, 2 H), 0.97–0.85 (m, 1 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 159.3 (d, $J=259.1$ Hz), 158.1, 147.0, 144.0, 142.4, 135.2, 134.2 (d, $J=7.7$ Hz), 131.6, 130.02 (d, $J=3.5$ Hz), 127.7 (d, $J=3.2$ Hz), 126.1, 122.5 (d, $J=21.4$ Hz), 122.0 (q, $J=272.7$ Hz), 120.62, 120.56, 120.3 (qd, $J=33.7, 12.5$ Hz), 118.4, 103.0, 67.9, 66.7, 60.3, 56.6, 56.3, 54.6, 38.1, 27.0, 23.8, 21.9 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ –60.85 (d, $J=12.5$ Hz, 3 F, CF_3), –110.5––110.8 (m, 1 F, $\text{C}_{\text{ar}}\text{F}$) ppm; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{29}\text{F}_4\text{N}_2\text{O}_2^+ [\text{M}-\text{Br}]^+$ 501.2160, found 501.2162.



(3ξ,9S)-9-Hydroxy-6'-methoxy-1-[2-nitro-4-(trifluoromethyl)benzyl]cinchonan-1-ium bromide

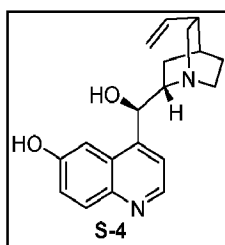
(PTC13): According to general procedure A, quinidine (649 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-2-nitro-4-(trifluoromethyl)benzene (568 mg, 2.00 mmol, 1.0 equiv) to give product **PTC13** (1.08 g, 1.78 mmol, 89% yield) as a white solid. **PTC13**: $R_f=0.40$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +209.8$ ($c=1.0$, CH_2Cl_2); m.p. = 196–198 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3352, 2945, 2833, 1622, 1591, 1578, 1543, 1508, 1472, 1460, 1433, 1414, 1352, 1325, 1291, 1261, 1242, 1228, 1206, 1182, 1161, 1137, 1093, 1022, 933, 916, 900, 863, 829, 781, 756, 718, 690 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.66 (d, $J=7.6$ Hz, 1 H), 8.61 (d, $J=4.0$ Hz, 1 H), 8.25 (s, 1 H), 7.95 (d, $J=7.7$ Hz, 1 H), 7.87 (d, $J=9.1$ Hz, 1 H), 7.71 (d, $J=3.9$ Hz, 1 H), 7.24 (d, $J=5.8$ Hz, 1 H), 7.12 (s, 1 H), 6.68 (d, $J=4.1$ Hz, 1 H), 6.51 (s, 1 H), 6.47 (d, $J=12.5$ Hz, 1 H), 5.94–5.83 (m, 1 H), 5.69 (d, $J=12.2$ Hz, 1 H), 5.19–5.05 (m, 2 H), 4.72–4.50 (m, 1 H), 3.95 (s, 3 H), 3.84 (s, 1 H), 3.76–3.66 (m, 1 H), 3.33 (ap t, $J=11.1$ Hz, 1 H), 2.97 (d, $J=8.7$ Hz, 1 H), 2.50 (d, $J=7.5$ Hz, 1 H), 2.46–2.36 (m, 1 H), 1.83 (s, 1 H), 1.77 (s, 1 H), 1.68 (d, $J=8.7$ Hz, 1 H), 0.96 (s, 1 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 158.7, 150.9, 147.6, 144.3, 142.3, 139.6, 135.2, 134.55 (q, $J=34.9$ Hz), 132.3, 131.09 (q, $J=3.1$ Hz), 125.6, 125.5, 123.32 (q, $J=3.5$ Hz), 122.3, 122.24 (q, $J=273.5$ Hz), 120.7, 119.5, 100.1, 70.6, 64.7, 57.7, 56.08, 56.06, 55.1, 38.4, 26.7, 24.2, 21.6 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ –62.4 (s) ppm; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{29}\text{F}_3\text{N}_3\text{O}_4^+ [\text{M}-\text{Br}]^+$ 528.2105, found 528.2103.



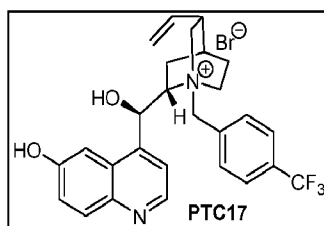
(3ξ,9S)-6',9-Dihydroxy-1-[4-(trifluoromethyl)benzyl]cinchonan-1-ium bromide (PTC15):

According to general procedure A, catalyst intermediate **S-3** (621 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-(trifluoromethyl)benzene (478 mg, 2.00 mmol, 1.0 equiv) to give product **PTC15** (989 mg, 1.80 mmol, 90% yield) as a white solid. **PTC15**: $R_f=0.25$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +176.0$ ($c=1.0$, MeOH); m.p. = 254–256 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3493, 3378, 3026, 2930, 2851, 1657,

1503, 1451, 1410, 1324, 1287, 1245, 1218, 1196, 1168, 1119, 1091, 1069, 1039, 1027, 1019, 1011, 990, 977, 933, 914, 881, 870, 862, 846, 826, 802, 775, 759, 729, 698, 689, 671 cm^{-1} ; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 10.10 (s, 1 H), 8.72 (d, $J=4.4$ Hz, 1 H), 8.06 (d, $J=8.0$ Hz, 2 H), 7.93 (d, $J=5.9$ Hz, 2 H), 7.92 (d, $J=7.0$ Hz, 1 H), 7.72 (d, $J=2.2$ Hz, 1 H), 7.66 (d, $J=4.4$ Hz, 1 H), 7.33 (dd, $J=9.1, 2.4$ Hz, 1 H), 6.75 (d, $J=4.0$ Hz, 1 H), 6.32 (s, 1 H), 5.98 (ddd, $J=17.4, 10.5, 7.0$ Hz, 1 H), 5.30 (d, $J=12.2$ Hz, 1 H), 5.19 (dd, $J=13.9, 8.8$ Hz, 2 H), 5.12 (d, $J=12.3$ Hz, 1 H), 4.21 (ddd, $J=11.3, 8.2, 2.2$ Hz, 1 H), 4.05 (dd, $J=11.4, 9.6$ Hz, 1 H), 3.95 (ap t, $J=9.4$ Hz, 1 H), 3.46 (ap t, $J=11.4$ Hz, 1 H), 3.01 (ap q, $J=10.0$ Hz, 1 H), 2.62 (ap q, 8.4 Hz, 1 H), 2.30–2.26 (mt, 1 H), 1.86 (s, 1 H), 1.81–1.69 (m, 2 H), 1.14–1.01 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 156.0, 146.7, 142.9, 142.6, 137.1, 134.8, 132.5, 131.4, 130.4 (q, $J=31.9$ Hz), 125.7 (q, $J=3.6$ Hz), 125.5, 124.0 (q, $J=272.4$ Hz), 121.8, 119.8, 117.0, 104.7, 67.3, 64.7, 61.2, 56.1, 53.9, 36.7, 26.3, 23.0, 20.6 ppm; ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -60.3 (s) ppm; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_2^+ [\text{M}-\text{Br}]^+$ 469.2097, found 469.2094.

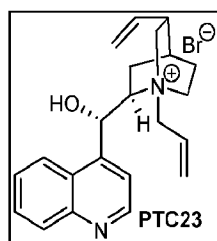


(3ξ,8α,9R)-Cinchonan-6',9-diol (**S-4**): Catalyst precursor **S-4** was prepared following a similar procedure as above starting from quinine (Shi *et al.*, 2007). To a stirred solution of quinine (3.25 g, 10.0 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL) flushed with argon was added a solution of BBr_3 (3.78 mL, 40.0 mmol, 4.0 equiv) in CH_2Cl_2 (30 mL) dropwise at -78°C . The reaction mixture was allowed to warm to 25°C and then refluxed at 40°C for 2 h. Then, the reaction was quenched by addition of 40% aq. NH_4OH solution (100 mL) at 0°C , followed by addition of H_2O (100 mL) and CH_2Cl_2 (100 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL), the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, $\text{EtOAc}:\text{Et}_3\text{N}:\text{MeOH}$, 50:1:2) to give precursor **S-4** (2.89 g, 9.30 mmol, 93% yield) as a yellow solid. The spectral data of this compound matched those reported in the literature (Li *et al.*, 2004).

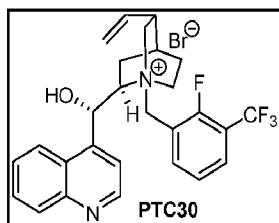


(3ξ,8α,9R)-6',9-Dihydroxy-1-[4-(trifluoromethyl)benzyl]cinchonan-1-ium bromide (**PTC17**): According to general procedure A, catalyst intermediate **S-4** (621 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-(trifluoromethyl)benzene (478 mg, 2.00 mmol, 1.0 equiv) to give product **PTC17** (989 mg, 1.82 mmol, 90% yield) as a white solid. **PTC17**: $R_f=0.25$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=-178.0$ ($c=1.0$, MeOH); m.p. = $259-260^\circ\text{C}$ (dec., $\text{MeOH}/\text{Et}_2\text{O}$); FT-IR (film) ν_{max} : 3210, 2953, 2851, 1621, 1534, 1466, 1423, 1408, 1327, 1238, 1221, 1161, 1122, 1068, 1037, 1018, 1003, 981, 927, 879, 863, 834, 783, 735, 691 cm^{-1} .

¹; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.16 (s, 1 H), 8.73 (d, *J*=4.2 Hz, 1 H), 8.02 (d, *J*=7.8 Hz, 2 H), 7.99–7.89 (m, 3 H), 7.68 (d, *J*=4.1 Hz, 1 H), 7.53 (s, 1 H), 7.36 (d, *J*=8.2 Hz, 1 H), 6.61 (d, *J*=3.8 Hz, 1 H), 6.39 (s, 1 H), 5.71 (ddd, *J*=17.1, 10.4, 6.5 Hz, 1 H), 5.37 (d, *J*=12.2 Hz, 1 H), 5.20 (d, *J*=17.3 Hz, 1 H), 5.11 (d, *J*=12.1 Hz, 1 H), 4.99 (d, *J*=10.5 Hz, 1 H), 4.28 (ap bt, 1 H), 3.94 (t, *J*=8.3 Hz, 1 H), 3.82 (d, *J*=11.2 Hz, 1 H), 3.32 (s, 1 H), 3.25–3.20 (m, 1 H), 2.67 (bs, 1 H), 2.18–2.13 (m, 1 H), 2.12–2.07 (m, 1 H), 2.00 (bs, 1 H), 1.82–1.77 (m, 1 H), 1.35 (ddd, *J*=16.6, 8.0, 3.1 Hz, 1 H) ppm; ¹³C NMR (151 MHz, DMSO-*d*₆) δ 156.0, 146.7, 143.0, 142.9, 138.0, 134.8, 132.7, 131.5, 130.4 (q, *J*=31.9 Hz), 125.7 (q, *J*=4.4 Hz), 125.5, 124.0 (q, *J*=272.4 Hz), 121.8, 119.9, 116.5, 104.3, 68.1 63.9, 61.9, 59.1, 50.7, 36.9, 25.8, 24.2, 20.5 ppm; ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ –55.6 (s) ppm; HRMS (ESI) calcd for C₂₇H₂₉BrF₃N₂O₂⁺ [*M*+H]⁺ 549.1359, found 549.1360.

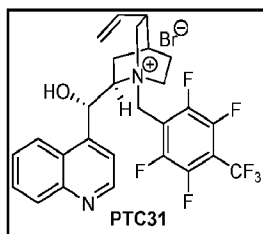


(3ξ,9S)-1-Allyl-9-hydroxycinchonan-1-ium bromide (PTC23): According to general procedure A, cinchonine (589 mg, 2.00 mmol, 1.0 equiv) was treated with allyl bromide (173 μL, 242 mg, 2.00 mmol, 1.0 equiv) to give product **PTC23** (756 mg, 1.84 mmol, 92% yield) as a white solid. **PTC23**: R_f=0.50 (silica gel, 10% MeOH in CH₂Cl₂); [α]_D²² = +147.5 (*c*=1.0, CH₂Cl₂); m.p.=234–236 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max}: 3379, 3180, 2952, 2882, 1639, 1616, 1590, 1571, 1509, 1460, 1423, 1388, 1340, 1314, 1296, 1262, 1235, 1209, 1164, 1123, 1094, 1052, 1038, 1021, 995, 951, 934, 894, 871, 815, 797, 776, 763, 719, 673 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.82 (d, *J*=4.4 Hz, 1 H), 8.12 (d, *J*=7.7 Hz, 1 H), 7.80–7.78 (m, 2 H), 7.33–7.28 (m, 2 H), 6.37 (bs, 2 H), 6.23–5.98 (m, 2 H), 5.86 (ddd, *J*=17.5, 10.5, 7.3 Hz, 1 H), 5.68 (d, *J*=9.8 Hz, 1 H), 5.40 (dd, *J*=11.7, 6.5 Hz, 1 H), 5.28–5.10 (m, 2 H), 4.84 (dd, *J*=12.1, 7.0 Hz, 1 H), 4.44 (t, *J*=10.1 Hz, 1 H), 3.94 (t, *J*=11.3 Hz, 1 H), 3.80 (ap t, *J*=9.3 Hz, 1 H), 3.58 (ap t, *J*=11.5 Hz, 1 H), 3.38 (ap q, *J*=9.6 Hz, 1 H), 2.60 (ap q, *J*=8.7 Hz, 1 H), 2.15 (ap t, *J*=11.2 Hz, 1 H), 1.90–1.73 (m, 2 H), 1.66 (ap q, *J*=10.5 Hz, 1 H), 0.78–0.70 (m, 1 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 149.8, 147.4, 144.4, 135.2, 130.3, 129.8, 128.7, 127.4, 125.0, 123.9, 123.0, 119.8, 118.0, 66.3, 64.9, 61.1, 56.3, 55.4, 38.0, 27.0, 23.7, 21.2 ppm; HRMS (ESI) calcd for C₂₂H₂₇N₂O⁺ [*M*–Br]⁺ 335.2118, found 335.2116.

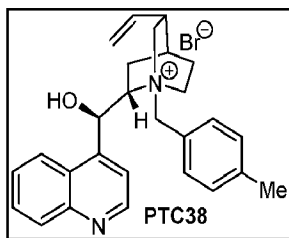


(3ξ,9S)-1-[2-Fluoro-3-(trifluoromethyl)benzyl]-9-hydroxycinchonan-1-ium bromide (PTC30): According to general procedure A, cinchonine (589 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene (514 mg, 2.00 mmol, 1.0 equiv) to give product **PTC30** (972 mg, 1.76 mmol, 88% yield) as a white solid. **PTC30**: R_f=0.35 (silica gel, 10% MeOH in CH₂Cl₂);

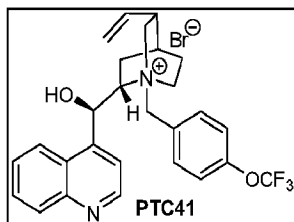
$[\alpha]_D^{22} = +158.7$ ($c=1.0$, MeOH); m.p. = 238–240 °C (dec., MeOH/Et₂O); FT-IR (film) $\nu_{\max}$: 3380, 3188, 2956, 2898, 1625, 1592, 1572, 1509, 1480, 1461, 1423, 1394, 1328, 1234, 1212, 1186, 1168, 1132, 1092, 1041, 1027, 1002, 1980, 935, 910, 874, 829, 812, 797, 777, 765, 749, 736, 687, 670 cm⁻¹; ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.99 (d, $J=4.4$ Hz, 1 H), 8.42 (d, $J=8.3$ Hz, 1 H), 8.29 (ap t, $J=6.9$ Hz, 1 H), 8.11 (d, $J=8.3$ Hz, 1 H), 8.05 (ap t, $J=7.0$ Hz, 1 H), 7.88–7.80 (m, 2 H), 7.75 (ap t, $J=7.5$ Hz, 1 H), 7.66 (ap t, $J=7.7$ Hz, 1 H), 6.90 (d, $J=3.4$ Hz, 1 H), 6.53 (s, 1 H), 6.02 (ddd, $J=17.4$, 10.4, 7.1 Hz, 1 H), 5.34–5.10 (m, 4 H), 4.25 (ddd, $J=11.1$, 8.3, 2.0 Hz, 1 H), 4.08–4.03 (m, 2 H), 3.43 (ap t, $J=11.1$ Hz, 1 H), 3.23 (ap q, $J=10.1$ Hz, 1 H), 2.66 (ap q, $J=8.2$ Hz, 1 H), 2.30 (ap t, $J=11.6$ Hz, 1 H), 1.89 (s, 1 H), 1.82–1.59 (m, 2 H), 1.10–1.03 (m, 1 H) ppm; ¹³C NMR (151 MHz, DMSO-*d*₆) δ 158.7 (d, $J=257.4$ Hz), 150.1, 147.6, 144.8, 140.7, 137.0, 130.0 (q, $J=4.4$ Hz), 129.7, 129.4, 127.2, 125.5 (d, $J=3.5$ Hz), 124.3, 123.9, 122.5 (q, $J=272.5$ Hz), 120.1, 117.49 (qd, $J=32.5$, 12.9 Hz), 117.47 (d, $J=12.6$ Hz), 117.0, 67.2, 64.8, 55.8, 55.1, 54.4, 36.8, 26.0, 23.0, 20.7 ppm; ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -58.95 (d, $J=13.0$ Hz, 3 F, CF₃), -133.7–-133.9 (m, 1 F, C_{ar}F) ppm; HRMS (ESI) calcd for C₂₇H₂₇F₄N₂O⁺ [*M*-Br]⁺ 471.2054, found 471.2068.



(3*ξ*,9*S*)-9-Hydroxy-1-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzyl]cinchon-1-ium bromide (PTC31): According to general procedure A, cinchonine (589 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene (334 μ L, 622 mg, 2.00 mmol, 1.0 equiv) give product **PTC31** (1.03 g, 1.70 mmol, 85% yield) as a white solid. **PTC31**: $R_f=0.15$ (silica gel, 10% MeOH in CH₂Cl₂); $[\alpha]_D^{22} = +129.2$ ($c=1.0$, MeOH); m.p. = 184–186 °C (dec., MeOH/Et₂O); FT-IR (film) $\nu_{\max}$: 3382, 3192, 2960, 2898, 1666, 1640, 1591, 1573, 1499, 1463, 1412, 1387, 1333, 1226, 1188, 1152, 1097, 1050, 1037, 1028, 1004, 962, 945, 873, 817, 798, 778, 763, 717, 685 cm⁻¹; ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.00 (d, $J=4.5$ Hz, 1 H), 8.45 (d, $J=8.4$ Hz, 1 H), 8.11 (d, $J=8.3$ Hz, 1 H), 7.87–7.84 (m, 2 H), 7.76 (ap t, $J=7.7$ Hz, 1 H), 7.00 (d, $J=3.4$ Hz, 1 H), 6.48 (d, $J=3.5$ Hz, 1 H), 6.02 (ddd, $J=17.3$, 10.4, 7.0 Hz, 1 H), 5.36 (d, $J=13.4$ Hz, 1 H), 5.28–5.17 (m, 3 H), 4.27–4.16 (m, 2 H), 3.92 (ap t, $J=10.9$ Hz, 1 H), 3.58 (ap t, $J=11.2$ Hz, 1 H), 3.50 (ap q, $J=9.7$ Hz, 1 H), 2.59 (ap q, $J=9.0$ Hz, 1 H), 2.25 (ap t, $J=12.0$ Hz, 1 H), 1.93–1.78 (m, 3 H), 1.06–0.98 (m, 1 H) ppm; ¹³C NMR (151 MHz, DMSO-*d*₆) δ 150.2, 147.6, 146.54 (dd, $J=251.7$, 13.8 Hz), 144.6, 143.85 (dd, $J=257.1$, 17.2 Hz), 136.8, 129.7, 129.5, 127.1, 124.4, 124.0, 120.5 (q, $J=274.9$ Hz), 120.2, 117.2, 112.85 (t, $J=16.5$ Hz), 110.8–110.0 (m), 67.2, 65.3, 56.3, 54.5, 50.4, 37.2, 25.6, 23.2, 20.9 ppm; ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -54.90 (t, $J=21.1$ Hz, 3 F, CF₃), -132.0 (bs, 2 F, 2 $\times$ C_{ar}F), -139.5 (bs, 2 F, 2 $\times$ C_{ar}F) ppm; HRMS (ESI) calcd for C₂₇H₂₄F₇N₂O⁺ [*M*-Br]⁺ 525.1771, found 525.1765.

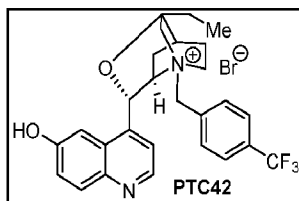


(3ξ,8α,9R)-9-Hydroxy-1-(4-methylbenzyl)cinchonan-1-ium bromide (PTC38): According to general procedure A, cinchonidine (589 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-methylbenzene (370 mg, 2.00 mmol, 1.0 equiv) to give product **PTC38** (873 mg, 1.82 mmol, 91% yield) as a white solid. **PTC38**: $R_f=0.50$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -185.2$ ($c=1.0$, CH_2Cl_2); m.p. = 226–228 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3199, 2945, 2821, 1640, 1615, 1590, 1571, 1509, 1481, 1459, 1420, 1409, 1389, 1345, 1318, 1265, 1233, 1221, 1208, 1191, 1163, 1116, 1060, 1027, 1007, 951, 943, 926, 898, 882, 858, 815, 803, 775, 755, 726, 697, 671 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.76 (d, $J=4.4$ Hz, 1 H), 8.15 (d, $J=8.1$ Hz, 1 H), 7.77 (d, $J=4.4$ Hz, 1 H), 7.60 (d, $J=7.9$ Hz, 1 H), 7.51 (d, $J=7.5$ Hz, 2 H), 7.14–7.08 (m, 2 H), 6.89 (d, $J=7.7$ Hz, 2 H), 6.54 (d, $J=5.9$ Hz, 1 H), 6.45 (s, 1 H), 5.92 (d, $J=12.0$ Hz, 1 H), 5.42 (d, $J=12.0$ Hz, 1 H), 5.37 (ddd, $J=16.8, 10.8, 6.1$ Hz, 1 H), 5.25 (d, $J=17.3$ Hz, 1 H), 4.86 (d, $J=10.5$ Hz, 1 H), 4.54 (dd, $J=16.9, 10.4$ Hz, 1 H), 4.11 (t, $J=9.0$ Hz, 1 H), 3.86 (d, $J=13.1$ Hz, 1 H), 3.09–3.04 (m, 2 H), 2.42 (s, 1 H), 2.26 (s, 3 H), 2.02 (dd, $J=15.9, 7.9$ Hz, 1 H), 1.86 (s, 1 H), 1.84–1.75 (m, 1 H), 1.53 (dd, $J=18.6, 11.7$ Hz, 1 H), 1.06–0.88 (m, 1 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 149.3, 146.9, 144.6, 139.8, 136.0, 133.9, 129.4, 129.1, 128.4, 127.3, 123.8, 123.5, 123.0, 119.7, 117.7, 66.7, 65.0, 61.9, 59.8, 50.1, 37.7, 26.4, 25.0, 22.3, 21.3 ppm; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}^+ [M-\text{Br}]^+$ 399.2431, found 399.2431.



(3ξ,8α,9R)-9-Hydroxy-1-[4-(trifluoromethoxy)benzyl]cinchonan-1-ium bromide (PTC41): According to general procedure A, cinchonidine (589 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-(trifluoromethoxy)benzene (320 μL , 510 mg, 2.00 mmol, 1.0 equiv) to give product **PTC41** (1.01 g, 1.84 mmol, 92% yield) as a white solid. **PTC41**: $R_f=0.40$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -138.0$ ($c=1.0$, CH_2Cl_2); m.p. = 234–236 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3197, 2999, 2950, 1640, 1612, 1591, 1571, 1509, 1482, 1462, 1421, 1390, 1307, 1253, 1219, 1205, 1161, 1115, 1061, 1037, 1022, 1003, 984, 925, 899, 881, 857, 829, 799, 775, 755, 733, 672 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.76 (d, $J=4.4$ Hz, 1 H), 8.20–8.08 (m, 1 H), 7.77 (d, $J=4.4$ Hz, 1 H), 7.74 (d, $J=7.9$ Hz, 2 H), 7.59–7.48 (m, 1 H), 7.03–7.01 (m, 2 H), 6.98 (d, $J=8.0$ Hz, 2 H), 6.49 (d, $J=5.8$ Hz, 1 H), 6.46–6.44 (m, 1 H), 6.19 (d, $J=12.2$ Hz, 1 H), 5.53 (d, $J=12.2$ Hz, 1 H), 5.37 (ddd, $J=15.6, 10.2, 5.4$ Hz, 1 H), 5.30 (d, $J=17.4$ Hz, 1 H), 4.88 (d, $J=9.8$ Hz, 1 H), 4.59 (ap q, $J=9.8$ Hz, 1 H), 4.17 (ap t, $J=8.7$ Hz, 1 H), 3.94 (ap dt, $J=12.9, 2.9$ Hz, 1 H), 3.03 (ap td, $J=12.0, 2.7$ Hz, 1 H), 2.98 (dd, $J=12.8, 10.7$ Hz, 1 H), 2.48 (bs, 1 H), 2.07–2.02 (m, 1 H), 1.91 (bs, 1 H), 1.83–1.74 (m, 1 H), 1.60

(ap q, $J=11.5, 11.5$ Hz, 1 H), 1.02–0.93 (m, 1 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 150.5, 149.2, 146.7, 144.3, 135.8, 135.7, 129.4, 128.3, 127.2, 125.3, 123.3, 122.6, 120.3 (q, $J=258.1$ Hz), 120.1, 119.6, 117.9, 66.8, 65.2, 60.7, 59.8, 50.2, 37.7, 26.3, 25.0, 22.5 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ –56.8 (s) ppm; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_2^+ [M-\text{Br}]^+$ 469.2097, found 469.2100.

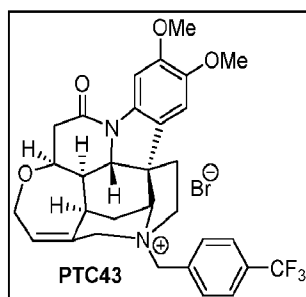


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(3ξ,9S)-6'-Hydroxy-1-[4-(trifluoromethyl)benzyl]-10,11-dihydro-3,9-epoxycinchonan-1-ium

bromide (PTC42): According to general procedure A, **PTC3** (621 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-(trifluoromethyl)benzene (478 mg, 2.00 mmol, 1.0 equiv) to give product **PTC42** (1.04 g, 1.90 mmol, 95% yield) as a white solid. **PTC42**: $R_f=0.50$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -37.2$ ($c=1.0$, CH_2Cl_2); m.p. = 226–228 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3407, 3085, 2984, 2949, 2912, 1620, 1589, 1529, 1496, 1479, 1463, 1444, 1427, 1399, 1375, 1363, 1331, 1284, 1240, 1221, 1156, 1125, 1117, 1096, 1068, 1041, 1021, 1010, 988, 936, 925, 910, 857, 848, 833, 791, 788, 763, 739, 703, 665 cm^{-1} ; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 10.45 (s, 1 H), 8.79 (d, $J=4.4$ Hz, 1 H), 8.14–7.94 (m, 5 H), 7.69 (d, $J=4.3$ Hz, 1 H), 7.38 (dd, $J=9.1, 2.3$ Hz, 1 H), 7.26 (d, $J=2.2$ Hz, 1 H), 6.81 (s, 1 H), 5.55 (d, $J=12.4$ Hz, 1 H), 5.01 (d, $J=12.4$ Hz, 1 H), 4.56 (d, $J=12.2$ Hz, 1 H), 4.47 (d, $J=6.3$ Hz, 1 H), 3.89 (dd, $J=18.7, 9.1$ Hz, 1 H), 3.60 (t, $J=6.5$ Hz, 1 H), 3.51 (d, $J=12.3$ Hz, 1 H), 3.29 (dd, $J=10.7, 9.2$ Hz, 1 H), 2.39 (s, 1 H), 1.78–1.62 (m, 5 H), 0.99 (ap t, $J=7.4$ Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 156.7, 147.4, 143.4, 139.2, 134.7, 133.2, 132.4, 130.96 (q, $J=31.9$ Hz), 126.4 (q, $J=3.9$ Hz), 126.2, 124.5 (q, $J=272.6$ Hz), 122.5, 120.0, 103.7, 76.6, 69.9, 69.6, 61.9, 60.3, 52.3, 32.3, 26.6, 22.6, 22.2, 7.4 ppm; ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ –60.3 (s) ppm; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_2^+ [M-\text{Br}]^+$ 469.2097, found 469.2109.

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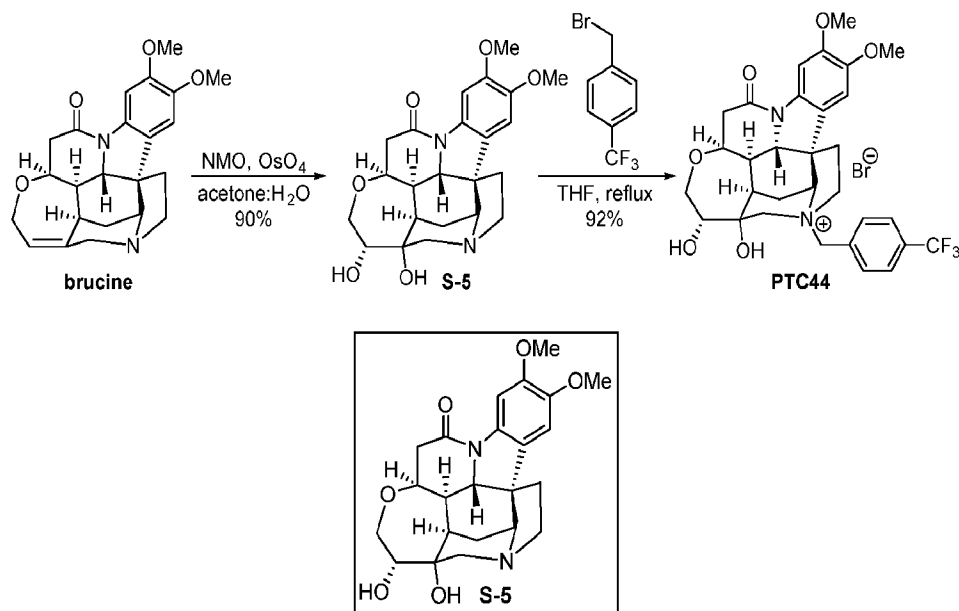


2,3-Dimethoxy-10-oxo-19-[4-(trifluoromethyl)benzyl]strychnidin-19-ium bromide (PTC43):

According to general procedure A, brucine (789 mg, 2.00 mmol, 1.0 equiv) was treated with 1-(bromomethyl)-4-(trifluoromethyl)benzene (478 mg, 2.00 mmol, 1.0 equiv) to give product **PTC43** (1.14 g, 1.80 mmol, 90% yield) as a white solid. **PTC43**: $R_f=0.60$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +66.2$ ($c=1.0$, CH_2Cl_2); m.p. = 235–237 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 2408, 2960, 2884, 2839, 1654, 1500, 1466, 1447, 1402, 1323, 1282, 1259, 1218, 1198, 1169, 1115, 1086, 1067, 1049, 1036, 1018, 990, 940, 896, 848, 829, 803, 784, 757, 729, 703, 690, 671 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.12 (d, $J=7.8$ Hz, 2 H), 7.69 (s, 1 H), 7.60 (d,

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5 $J=7.9\text{ Hz}$, 2H), 6.90 (s, 1H), 6.27 (s, 1H), 5.94 (d, $J=12.4\text{ Hz}$, 1H), 5.78 (d, $J=12.4\text{ Hz}$, 1H), 4.86 (d, $J=12.9\text{ Hz}$, 1H), 4.70 (s, 1H), 4.34–4.26 (m, 1H), 4.26–4.11 (m, 2H), 3.98 (dd, $J=14.2$, 5.5 Hz, 1H), 3.93–3.80 (m, 8H), 3.48 (ap td, $J=13.4$, 5.4 Hz, 1H), 3.25 (s, 1H), 3.21 (d, $J=15.7\text{ Hz}$, 1H), 3.08 (dd, $J=17.9$, 8.4 Hz, 1H), 2.61 (dd, $J=17.8$, 1.9 Hz, 1H), 2.00 (ap td, $J=13.8$, 7.0 Hz, 1H), 1.92–1.83 (m, 1H), 1.63 (d, $J=15.1\text{ Hz}$, 1H), 1.30 (d, $J=10.4\text{ Hz}$, 1H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 168.2, 150.3, 146.7, 136.7, 135.3, 134.2, 132.8 (q, $J=33.0\text{ Hz}$), 132.6, 132.4, 125.9 (q, $J=3.2\text{ Hz}$), 123.2 (q, $J=272.6\text{ Hz}$), 118.2, 105.6, 100.8, 77.2, 72.0, 67.0, 64.0, 63.5, 59.1, 57.7, 57.1, 56.2, 52.7, 46.9, 41.9, 39.7, 29.9, 25.7 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ –62.2 (s) ppm; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{32}\text{F}_3\text{N}_2\text{O}_4^+ [\text{M}-\text{Br}]^+$ 553.2309, found 553.2309.

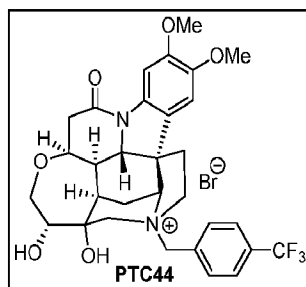


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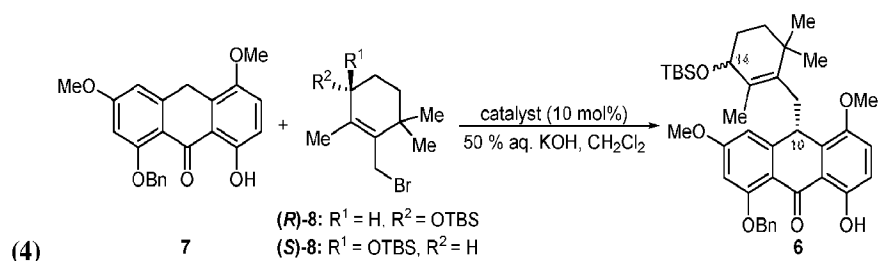
(22a)-21,22-Dihydroxy-2,3-dimethoxy-21,22-dihydrostrychnidin-10-one (S-5): The dihydroxylation of brucine was prepared following a literature procedure (Kim *et al.*, 2009). To a stirred solution of brucine (5.00 g, 11.6 mmol, 1.0 equiv) in a mixture of acetone (45 mL), *tert*-butanol (2.5 mL), and H_2O (2.5 mL), was added 4-methylmorpholine *N*-oxide monohydrate (1.73 g, 12.8 mmol, 1.1 equiv) followed by dropwise addition of osmium tetroxide (500 μL , 69.6 μmol , 4 wt% in water, 0.006 equiv). The resulting suspension was stirred for 24 h, after which time the resulting solids were collected by filtration. The solids were washed with dichloromethane ($2 \times 80\text{ mL}$) and dried under high vacuum for 24 h to give analytically pure brucine-diol S-5 (4.50 g, 10.4 mmol, 90% yield). The physical and spectroscopic data of this compound matched those reported in the literature (Kim *et al.*, 2009).

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(22a)-21,22-Dihydroxy-2,3-dimethoxy-10-oxo-19-[4-(trifluoromethyl)benzyl]-21,22-

dihydrostrychnidin-19-ium bromide (PTC44): According to general procedure A, brucine-diol **S-5** (857 mg, 2.00 mmol, 1.0equiv) was treated with 1-(bromomethyl)-4-(trifluoromethyl)benzene (478 mg, 2.00 mmol, 1.0equiv) to give product **PTC44** (1.23 g, 1.84 mmol, 92% yield) as a white solid. **PTC44**: $R_f=0.30$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=+79.0$ ($c=1.0$, CH_2Cl_2); m.p.=248–250 °C (dec., MeOH/Et₂O); FT-IR (film) ν_{max} : 3493, 3378, 3026, 2930, 2851, 1657, 1503, 1451, 1410, 1324, 1287, 1245, 1218, 1196, 1168, 1119, 1091, 1069, 1039, 1027, 1019, 1011, 990, 977, 933, 914, 881, 870, 862, 846, 826, 802, 775, 759, 729, 698, 689, 671 cm^{-1} ; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.02 (d, $J=7.9$ Hz, 2H), 7.86 (d, $J=8.1$ Hz, 2H), 7.66 (s, 1H), 7.54 (s, 1H), 5.71 (d, $J=6.2$ Hz, 1H), 5.57 (s, 1H), 5.53 (d, $J=12.2$ Hz, 1H), 5.09 (d, $J=12.1$ Hz, 1H), 4.89 (s, 1H), 4.54–4.49 (m, 2H), 4.19 (dd, $J=12.6$, 6.6 Hz, 1H), 3.92–3.84 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.56 (dd, $J=13.4$, 6.8 Hz, 1H), 3.46–3.44 (m, 1H), 3.24 (s, 1H), 3.05 (ap t, $J=9.5$ Hz, 1H), 2.97 (d, $J=15.2$ Hz, 1H), 2.88 (d, $J=15.3$ Hz, 1H), 2.78–2.60 (m, 3H), 2.47 (d, $J=1.5$ Hz, 1H), 2.40 (s, 1H), 2.10 (ap t, $J=11.9$ Hz, 1H), 1.83–1.76 (m, 1H), 1.72 (d, $J=15.2$ Hz, 1H) ppm; ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 168.5, 149.3, 146.5, 134.2, 134.0, 133.6, 130.4 (q, $J=32.0$ Hz), 125.8 (q, $J=3.4$ Hz), 124.0 (q, $J=272.4$ Hz), 122.7, 107.6, 99.8, 72.60, 72.57, 72.1, 71.6, 65.9, 64.2, 62.4, 61.9, 57.3, 56.6, 55.7, 50.4, 48.5, 40.0, 38.8, 31.7, 23.1 ppm; ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ –60.4 (s) ppm; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{34}\text{F}_3\text{N}_2\text{O}_6^+$ $[M-\text{Br}]^+$ 587.2363, found 587.2367.

(3) Asymmetric Alkylation of Anthrone 7 and Allylic Bromide 6 with Different Catalysts

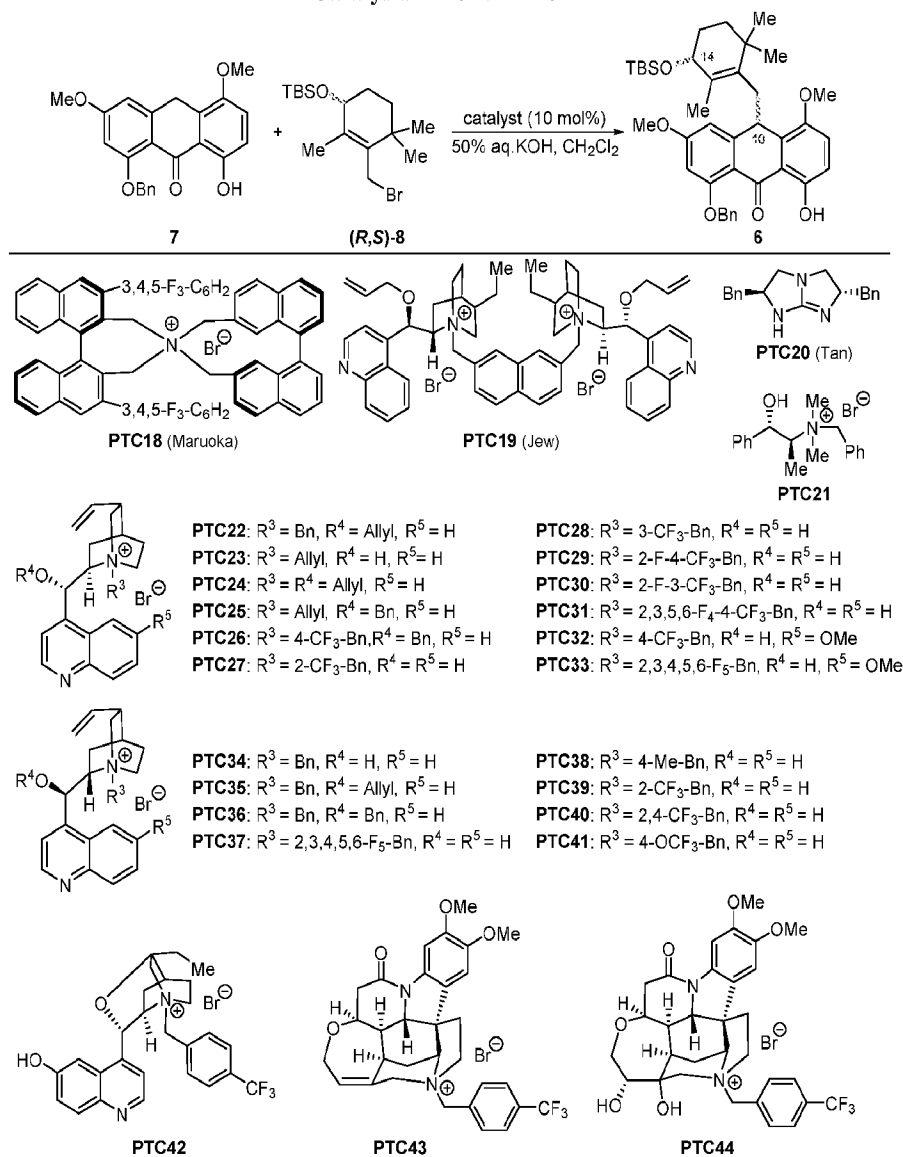
General procedure for asymmetric alkylation of anthrone: To a mixture of anthrone **7** (37.6 mg, 100 μmol , 1.0 equiv), allylic bromide **8** [(*R,S*)-, (*R*)- or (*S*)-; 38.2 mg, 110 μmol , 1.1 equiv] and **PTC** catalyst (phase transfer catalyst, 10.0 μmol , 10 mol%, 0.1 equiv) in CH_2Cl_2 (1.0 mL) under argon, was added 50% aq. KOH solution (0.3 mL) dropwise at –78 °C. The reaction mixture was stirred vigorously and then allowed to warm to 0 °C. Stirring was continued at this temperature for 8 h. The mixture was then quenched by addition of water (10 mL) and extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 , filtered, and concentrated to give a crude oil, which was purified by flash column chromatography on silica gel (2% $\rightarrow$ 5% $\rightarrow$ 10% EtOAc:hexanes) to give enantioenriched alkylated anthrone **6** as a yellow foam.

General procedure for preparing racemic alkylated anthrone: To a solution of anthrone **7** (37.6 mg, 100 μmol , 1.0 equiv), allylic bromide **8** [(*R,S*)-, (*R*)- or (*S*)-; 38.2 mg, 110 μmol , 1.1 equiv] in DMF (1 mL) under argon, was added Na_2CO_3 (10.6 mg, 1.00 mmol, 10 equiv). The reaction mixture was shielded from light and stirred vigorously for 1 h in the dark. The reaction was quenched by addition of water (10 mL) and was then further diluted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (2 $\times$ 10 mL), and the

combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a crude oil, which was purified by flash column chromatography on silica gel (2%→5%→10% EtOAc:hexanes) to give racemic alkylated anthrone **6** as a yellow foam.

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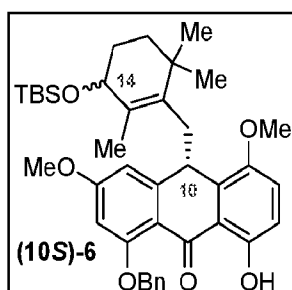
Table 1. Additional Results for the Asymmetric Alkylation of Anthrone **7 with Allylic Bromides **8** Using Catalysts PTC18–PTC44.^a**



Entry	Catalyst	Con. (%)	Yield(%)	dr(%) ^b
1	PTC17	80	70	52:48
2	PTC18	>99	75	53:47
3	PTC19	60	68	54:46
4	PTC20	>99	77	61:39
5	PTC21	>99	76	55:45
6	PTC22	>99	74	58:42
7	PTC23	>99	76	57:43
8	PTC24	>99	73	62:38
9	PTC25	80	70	65:35
10	PTC26	>99	72	63:37
11	PTC27	>99	70	58:42
12	PTC28	>99	72	79:21
13	PTC29	>99	75	55:45
14	PTC30	>99	76	56:44

15	PTC31	>99	75	51:49
16	PTC32	>99	76	61:19
17	PTC33	>99	77	43:57
18	PTC34	>99	76	47:53
19	PTC35	>99	75	49:51
20	PTC36	>99	75	42:58
21	PTC37	>99	75	39:61
22	PTC38	>99	72	27:73
23	PTC39	>99	70	32:68
24	PTC40	>99	72	30:70
25	PTC41	>99	75	64:36
26	PTC42	>99	77	42:58
29	PTC43	>99	78	56:44

^aReaction conditions: anthrone **5** (0.1 mmol), allylic bromide **6** (0.11 mmol), PTC catalyst (10 mol%), CH₂Cl₂ (0.9 mL), 50% aq KOH (0.3 mL), -78 °C to 0 °C, 8 h. ^b The diastereomeric ratio (er) was determined by HPLC using chiralPak AD-H column.



5 **(10S)-1-(Benzyloxy)-10-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethyl-cyclohex-1-en-1-yl)methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10*H*)-one** [enantioenriched **(10S)-6**]: yellow foam, 48.2 mg, 75.0 μmol, 75% yield, 86:14 dr. Diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.24 min for **(10*R*,14*S*)-6**; 5.46 min for **(10*R*,14*R*)-6**; 5.94 min for **(10*S*,14*R*)-6**; 8.48 min for **(10*S*,14*S*)-6**.

10 The dr ratios with respect to the newly established stereochemistry at C-10 (viridicatumtoxin numbering) for all entries using racemic allylic bromide **(*R,S*)-8** were determined from the HPLC peak areas corresponding to **(10*S*)-6**:**(10*R*)-6**. Thus, the diastereomeric ratio regarding the stereoselectivity at C-10 for the experiment listed within the manuscript (Table 1, entry 15) using racemic allylic bromide **(*R,S*)-8** was calculated as follows using data derived from the acquired HPLC chromatogram (*vide infra*):

$$15 \quad \text{dr} = \frac{[(10*S*,14*R*)-6 + (10*S*,14*S*)-6] : [(10*R*,14*S*)-6 + (10*R*,14*R*)-6]}{(50.764\% + 35.269\%) : (6.704\% + 7.262\%)} = 86.033\% : 13.966\%$$

approximated to 86 : 14.

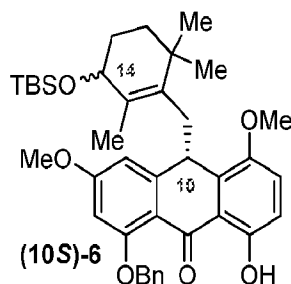
[Note: The dr value that can be deduced from the ¹H NMR spectra represents a different ratio of stereoisomers due to the lack of differentiation of enantiomers in standard ¹H NMR experiments. Thus, the following ratio can be calculated using ¹H NMR data:

$$\frac{\text{first pair of enantiomers}}{[(10*S*,14*R*)-6 + (10*R*,14*S*)-6] : [(10*S*,14*S*)-6 + (10*R*,14*R*)-6]} \quad \frac{\text{second pair of enantiomers}}{}$$

$$= (50.764\% + 6.704\%) : (35.269\% + 7.262\%) = 57.468\% : 42.531\%$$

approximated to 57.5 : 42.5.

Finally, in contrast to the dr ratio calculation explained above (using the HPLC traces), the NMR derived value does not allow for any judgement concerning the obtained stereoselectivity at C-10.]

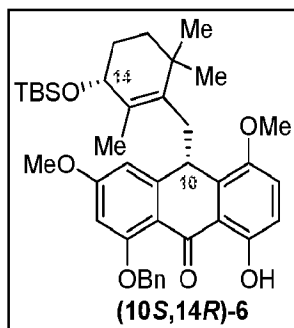


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Enantioenriched **(10S)-6**: $R_f=0.50$ (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}=+71.9$ ($c=1.0$, CH_2Cl_2 , 86:14 dr); FT-IR (film) ν_{max} : 2932, 2856, 1636, 1599, 1583, 1568, 1472, 1432, 1328, 1265, 1227, 1196, 1164, 1148, 1101, 1034, 1002, 907, 832, 772, 728 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond. ^1H NMR (600 MHz, CDCl_3) δ 12.70 (s, 1 H, minor), δ 12.69 (s, 1 H, major), 7.57 (d, $J=7.5$ Hz, 2 H, major + minor), 7.47–7.35 (m, 2 H, major + minor), 7.35–7.27 (m, 1 H, major + minor), 7.06 (d, $J=9.0$ Hz, 1 H, minor), 7.05 (d, $J=8.9$, 1 H, major), 6.860 (d, $J=8.9$ Hz, 1 H, minor), 6.856 (d, $J=8.9$ Hz, 1 H, major), 6.44 (d, $J=2.2$ Hz, 1 H, major), 6.43 (d, $J=2.3$ Hz, 1 H, minor), 6.42 (s, 1 H, major), 6.30 (s, 1 H, minor), 5.25 (ABq, $\Delta\delta_{\text{AB}}=0.067$, $J=12.7$ Hz, 2 H, major + minor), 4.64 (s, 1 H, major), 4.56 (s, 1 H, minor), 3.97 (s, 1 H, major), 3.86 (s, 1 H, minor), 3.90 (s, 3 H, minor), 3.89 (s, 3 H, major), 3.84 (s, 3 H), 2.68 (d, $J=12.5$ Hz, 1 H, major + minor), 2.20–0.65 (m, 14 H, major + minor), 0.91 (s, 9 H, major), 0.88 (s, 9 H, minor), 0.10 (s, 3 H, minor), 0.05 (s, 3 H, major), 0.08 (s, 3 H, major), 0.01 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* δ 188.60 (major), 188.55 (minor), 163.75 (major), 163.67 (minor), 161.97 (major), 161.86 (minor), 150.3 (b, major), 149.6 (b, minor), 156.29 (major), 156.26 (minor), 147.72 (major), 147.62 (minor), 136.73 (minor), 136.70 (major), 133.63 (minor), 133.45 (major), 128.69 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.78 (major), 117.74 (minor), 117.71 (major), 117.69 (minor), 115.09 (major), 115.05 (minor), 106.73 (b, major), 106.51 (b, minor), 100.19 (b, minor), 100.10 (b, major), 70.8 (major + minor), 56.08 (minor), 56.04 (major), 55.75 (major), 55.57 (minor), 41.12 (major), 40.62 (minor), 35.9 (major + minor), 29.76 (major), 29.69 (minor), 29.08 (major), 28.91 (minor), 26.08 (minor), 26.05 (major), 18.3 (major), 16.6 (minor), –4.0 (major), –4.2 (minor), –4.64 (major), –4.67 (minor) ppm; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{50}\text{O}_6\text{SiNa}^+ [M+\text{Na}]^+$ 665.3269, found 665.3274. *Due to signal broadening, not all the ^{13}C signals could be identified.

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(10S)-1-(Benzyloxy)-10-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethyl-cyclohex-1-en-1-

yl)methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10*H*)-one [enantioenriched **(10S,14R)-6**]: yellow foam,

48.2 mg, 75.0 μ mol, 75% yield, 89:11 dr. Diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}$ C

5 , flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.97 min for **(10R,14R)-6**; 6.74 min for **(10S,14R)-6**.

Enantioenriched **(10S,14R)-6**: R_f =0.50 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +85.2 (c =1.0, CH_2Cl_2 , 89:11

dr); FT-IR (film) ν_{max} : 2932, 2856, 1636, 1599, 1583, 1568, 1472, 1432, 1328, 1265, 1227, 1196, 1164, 1148,

1101, 1034, 1002, 907, 832, 772, 728 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and

^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.68

10 (s, 1 H, major + minor), 7.57 (d, J =7.4 Hz, 2 H, major + minor), 7.39 (ap t, J =7.7 Hz, 2 H, major + minor), 7.30

(ap t, J =7.4 Hz, 1 H, major + minor), 7.05 (d, J =9.0 Hz, 1 H, major + minor), 6.86 (d, J =8.9 Hz, 1 H, major +

minor), 6.44 (d, J =2.2 Hz, 1 H, major), 6.43 (d, J =2.2 Hz, 1 H, minor), 6.40 (b, 1 H, major), 6.29 (b, 1 H, minor),

5.25 (ABq, $\Delta\delta_{\text{AB}}$ =0.072, J =12.6 Hz, 2 H, major + minor), 4.64 (b, 1 H, major + minor), 3.97 (b, 1 H, major +

minor), 3.90 (s, 3 H, minor), 3.89 (s, 3 H, major), 3.84 (s, 3 H, major + minor), 2.70 (d, J =10.9 Hz, 1 H, major +

15 minor), 2.10–0.64 (m, 14 H, major + minor), 0.92 (s, 9 H, major), 0.91 (s, 9 H, minor), 0.10 (s, 3 H, major), 0.07

(s, 3 H, major), 0.04 (s, 3 H, minor), 0.01 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* δ 188.60 (major),

188.55 (minor), 163.74 (major), 163.66 (minor), 161.97 (major), 161.86 (minor), 156.29 (major), 156.26

(minor), 150.30 (b, major + minor), 147.72 (major), 147.62 (minor), 136.72 (minor), 136.69 (major), 133.63

(minor), 133.45 (major), 128.69 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.78 (major),

20 117.74 (minor), 117.71 (major), 117.69 (minor), 115.09 (major), 115.05 (minor), 106.73 (b, major), 106.51 (b,

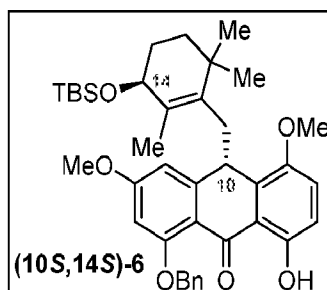
minor), 100.11 (b, major + minor), 72.7 (b, major + minor), 70.8 (major + minor), 56.08 (minor), 56.04 (major),

55.75 (major), 55.57 (minor), 41.1 (b, major + minor), 38.70 (b, major + minor), 35.94 (major + minor), 29.76

(major), 29.69 (minor), 29.09 (major), 28.91 (minor), 26.07 (minor), 26.04 (major), 18.34 (major + minor), –4.0

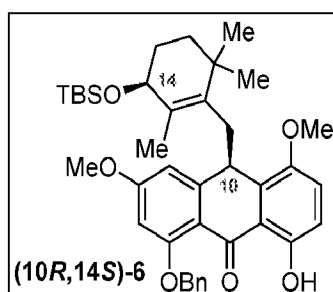
(major), –4.2 (minor), –4.65 (major + minor) ppm; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{50}\text{O}_6\text{SiNa}^+$ [$M+\text{Na}$] $^+$ 665.3269,

25 found 665.3269. *Due to signal broadening, not all the ^{13}C signals could be identified.



(10S)-1-(Benzyloxy)-10-[[[(3S)-3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [enantioenriched (10S,14S)-6]: yellow foam, 48.2 mg, 75.0 μ mol, 75% yield, 83:17 dr. Diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}$ C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.35 min for (10R,14S)-6; 8.74 min for (10S,14S)-6.

- 5 Enantioenriched (10S,14S)-6: R_f =0.50 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +55.4 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2932, 2856, 1636, 1599, 1583, 1568, 1472, 1432, 1328, 1265, 1227, 1196, 1164, 1148, 1101, 1034, 1002, 907, 832, 772, 728 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR) due to hindered bond rotation of the newly-formed C–C bond. ¹H NMR (600 MHz, CDCl₃) δ 12.69 (s, 1 H, major), 12.68 (s, 1 H, minor), 7.56 (d, J =7.6 Hz, 2 H, major + minor), 7.39 (ap t, J =7.6 Hz, 2 H, major + minor), 7.29 (ap t, J =7.4 Hz, 1 H, major + minor), 7.06 (d, J =9.0 Hz, 1 H, major + minor), 6.86 (d, J =8.9 Hz, 1 H, major + minor), 6.44 (d, J =2.2 Hz, 1 H, minor), 6.43 (d, J =2.2 Hz, 1 H, major), 6.40 (b, 1 H, minor), 6.30 (d, J =1.7 Hz, 1 H, major), 5.25 (ABq, $\Delta\delta_{AB}$ =0.073, J =12.6 Hz, 2 H, major + minor), 4.57 (b, 1 H, major + minor), 3.90 (s, 3 H, major), 3.89 (s, 3 H, minor), 3.87–3.78 (b, 1 H, major + minor), 3.83 (s, 3 H, major + minor), 2.68 (d, J =11.1 Hz, 1 H, major + minor), 2.10–0.64 (m, 14 H, major + minor), 0.92 (s, 9 H, minor), 0.88 (s, 9 H, major), 0.10 (s, 3 H, minor), 0.08 (s, 3 H, minor), 0.04 (s, 3 H, major), 0.01 (s, 3 H, major); ¹³C NMR (151 MHz, CDCl₃)* δ 188.60 (minor), 188.55 (major), 163.66 (major + minor), 161.97 (minor), 161.87 (major), 156.29 (minor), 156.26 (major), 149.7 (b, major + minor), 147.72 (minor), 147.62 (major), 136.72 (major), 136.69 (minor), 133.63 (major), 133.45 (minor), 128.7 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.78 (minor), 117.74 (major), 117.69 (major + minor), 115.09 (minor), 115.05 (major), 106.51 (b, major + minor), 100.11 (b, major + minor), 71.7 (b, major + minor), 70.7 (major + minor), 56.09 (major), 56.04 (minor), 55.75 (minor), 55.57 (major), 40.6 (b, major + minor), 36.48 (b, major + minor), 35.93 (major + minor), 29.76 (minor), 29.69 (major), 29.11 (minor), 28.91 (major), 26.06 (major), 26.05 (minor), 18.34 (major + minor), 16.58 (major + minor), -4.02 (minor), -4.18 (major), -4.67 (major + minor) ppm; HRMS (ESI) calcd for C₃₉H₅₀O₆SiNa⁺ [M +Na]⁺ 665.3269, found 665.3272. *Due to signal broadening, not all the ¹³C signals could be identified.

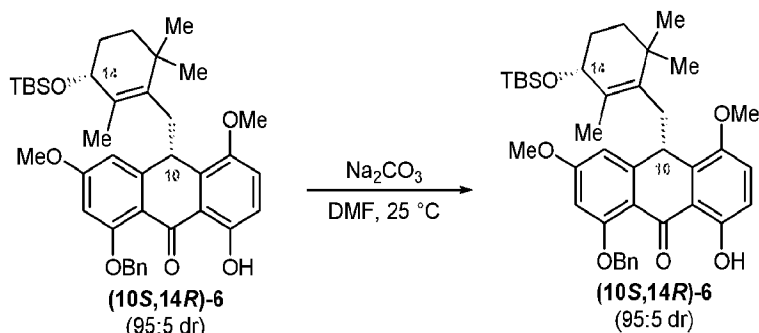
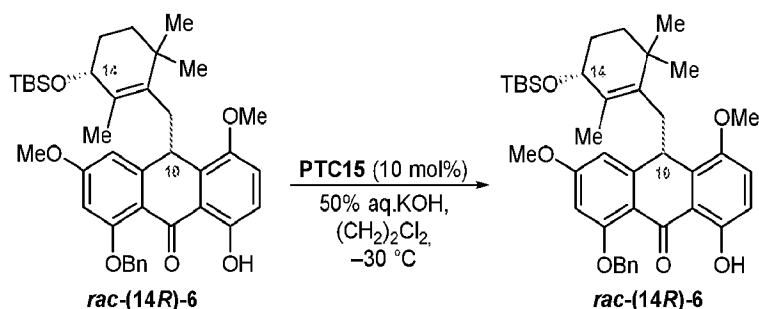


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(10R)-1-(Benzyloxy)-10-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl)methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [enantioenriched (10R,14S)-6]: yellow foam, 48.9 mg, 76.0 μ mol, 76% yield, 13:87 dr. Diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}$ C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.44 min for (10R,14S)-6; 9.52 min for (10S,14S)-6.

- 30 Enantioenriched (10R,14S)-6: R_f =0.50 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = -82.8 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2932, 2856, 1636, 1599, 1583, 1568, 1472, 1432, 1328, 1265, 1227, 1196, 1164, 1148, 1101, 1034, 1002, 907, 832, 772, 728 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR)

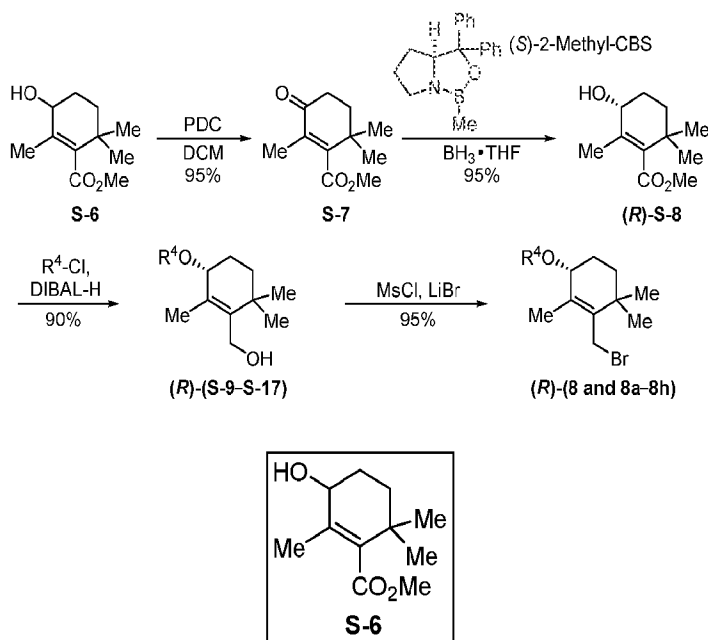
due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.71 (s, 1 H, minor), 12.70 (s, 1 H, major), 7.57 (d, $J=7.4$ Hz, 2 H, major + minor), 7.39 (ap t, $J=7.7$ Hz, 2 H, major + minor), 7.30 (ap t, $J=7.4$ Hz, 1 H, major + minor), 7.05 (d, $J=9.0$ Hz, 1 H, major + minor), 6.86 (d, $J=8.9$ Hz, 1 H, major + minor), 6.44 (d, $J=2.3$ Hz, 1 H, major), 6.43 (d, $J=2.3$ Hz, 1 H, minor), 6.39 (b, 1 H, major), 6.29 (b, 1 H, minor), 5.25 (ABq, $\Delta\delta_{\text{AB}}=0.068$, $J=12.6$ Hz, 2 H, major + minor), 4.64 (b, 1 H, major), 4.56 (b, 1 H, minor), 3.97 (b, 1 H, major + minor), 3.90 (s, 3 H, minor), 3.89 (s, 3 H, major), 3.84 (s, 3 H, major + minor), 2.69 (b, 1 H, major + minor), 2.10–0.67 (m, 14 H, major + minor), 0.92 (s, 9 H, major), 0.88 (s, 9 H, minor), 0.10 (s, 3 H, major), 0.08 (s, 3 H, major), 0.05 (s, 3 H, minor), 0.01 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* δ 188.60 (major), 188.55 (minor), 163.75 (major), 163.67 (minor), 161.97 (major), 161.86 (minor), 156.30 (major), 156.27 (minor), 150.22 (b, major + minor), 147.72 (major), 147.62 (minor), 136.74 (minor), 136.71 (major), 133.62 (minor), 133.44 (major), 128.69 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.77 (major + minor), 117.71 (major), 117.69 (minor), 115.09 (major), 115.07 (minor), 106.73 (b, major), 106.52 (b, minor), 100.10 (b, major + minor), 72.7 (b, major + minor), 70.7 (major + minor), 56.07 (minor), 56.03 (major), 55.75 (major), 55.57 (minor), 41.1 (b, major + minor), 38.7 (b, major + minor), 35.92 (major + minor), 29.76 (major), 29.70 (minor), 29.09 (major), 28.91 (minor), 26.08 (minor), 26.06 (major), 18.34 (major + minor), –4.0 (major), –4.2 (minor), –4.63 (major + minor) ppm; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{50}\text{O}_6\text{SiNa}^+$ $[M+\text{Na}]^+$ 665.3269, found 665.3269. *Due to signal broadening, not all the ^{13}C signals could be identified.



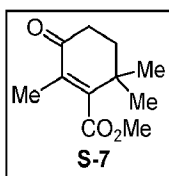
To check the potential problem associated with C10 racemization of the alkylation product, two verification experiments were carried out as shown above. Thus, alkylated racemic (14R)-6 was subjected to the same asymmetric alkylation conditions [1.0 mol% **PTC15**, 40% aq. Cs_2CO_3 , $(\text{CH}_2)_2\text{Cl}_2$, -20°C , 72 h]. Under these conditions no enrichment of the recovered starting material was observed, indicating that the asymmetric induction occurs in the alkylation step rather than being a result of deprotonation/asymmetric

protonation of the initially formed substituted anthrone. In a second experiment an enriched sample of alkylated product (**10S,14R**)-**6** (95:5 dr) were utilized, but this time under racemic conditions (Na_2CO_3 , DMF, 25 °C, 1 h) and observed no change in the dr ratio, again indicating that the asymmetric induction in the system occurs at the alkylation state rather than a subsequent equilibration step.

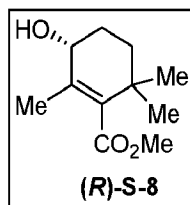
5 Allylic Bromides Synthesis



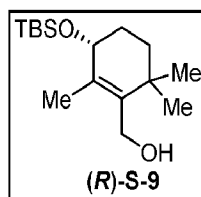
Methyl 3-hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (S-6): Allylic alcohol **S-6** was prepared using the published four-step procedure starting from geranic acid (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). The physical and spectroscopic data of this compound matched those reported in the literature (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014).



Methyl 2,6,6-trimethyl-3-oxocyclohex-1-ene-1-carboxylate (S-7): Following the general procedure for PDC oxidation of alcohols (Corey and Schmidt, 1979), enone **S-7** was prepared. To a solution of allylic alcohol **S-6** (9.92 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) was added pyridinium dichromate (PDC, 28.2 g, 75.0 mmol, 1.5 equiv) in one portion at 0 °C, and then the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was passed through a pad of silica gel, eluted with 20% EtOAc:hexanes to give enone **S-7** as colorless oil (9.32 g, 47.5 mmol, 95% yield). The physical and spectroscopic data of this compound matched those reported in the literature (Heather *et al.*, 1976).

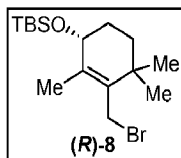


Methyl (3R)-3-hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxylate [(R)-S-8]: According to general procedure of CBS reduction of ketones (Corey *et al.*, 1987), chiral allylic alcohol **(R)-S-8** was prepared. To a solution of (S)-(-)-2-methyl-CBS-oxazaborolidine (831 mg, 3.00 mmol, 0.1 equiv) in THF (60 mL) was added $\text{BH}_3 \cdot \text{THF}$ (30.0 mL, 30.0 mmol, 1 M solution in THF, 1.0 equiv) at 0 °C, and the solution was stirred for 15 min. A solution of enone **S-7** (5.89 g, 30.0 mmol, 1.0 equiv) in THF (60 mL) was then added dropwise at 0 °C, and the resulting mixture was stirred at this temperature for 1 h. The reaction was then quenched by addition of MeOH (10 mL), concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (10% → 20% → 40% EtOAc:hexanes) to give chiral allylic alcohol **(R)-S-8** [5.65 g, 28.5 mmol, 95% yield, 94% ee (determined by ^1H NMR spectroscopic analysis of its mosher ester)] as a colorless oil. The physical and spectroscopic data of this compound matched those reported in the literature (Yoshikawa *et al.*, 1996).



[(3R)-3-[[*tert*-Butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methanol [(R)-S-9]: Following the reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014), chiral OTBS ether alcohol **(R)-S-9** was prepared. Chiral allylic alcohol **(R)-S-8** (1.56 g, 7.80 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (80 mL) at 25 °C. Imidazole (1.06 g, 15.6 mmol, 2.0 equiv) and TBSCl (1.90 g, 12.6 mmol, 1.6 equiv) were added sequentially, and the suspension was stirred at 25 °C for 12 h. The reaction was quenched by addition of saturated NaHCO_3 solution (50 mL), and the phases were separated. The organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. Residual volatiles were then azeotropically removed with toluene (twice). The crude OTBS ether was dissolved in CH_2Cl_2 (70 mL) and the solution was cooled to -78 °C. DIBAL-H (21.0 mL, 1.0 M solution in hexanes, 21.0 mmol, 2.7 equiv) was added to the stirred reaction mixture over 20 minutes. Then, the reaction mixture was allowed to warm to 0 °C and was stirred at this temperature for 70 min, and then cautiously quenched by addition of methanol (10 mL). The mixture was allowed to warm to 25 °C, and saturated aq. Rochelle salt solution (80 mL) was added. The resulting thick emulsion was vigorously stirred at 25 °C for 5 h. The phases were separated, and the organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% → 10% → 15% EtOAc:hexanes) to give chiral OTBS ether alcohol **(R)-S-9** (2.12 g, 7.21 mmol, 91% for two steps) as a colorless oil. **(R)-S-9**: R_f = 0.20 (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = -19.2$ (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} : 3451, 2953, 2929, 2857, 1472, 1462, 1361, 1253, 1084, 1061, 1033, 1005, 985, 933, 886, 834, 815, 773, 669 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.14 (d, J = 11.4 Hz, 1 H), 4.09 (d, J = 11.4 Hz, 1 H), 4.00 (ap

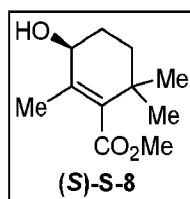
t, $J=5.8$ Hz, 1 H), 1.87–1.74 (m, 4 H), 1.65–1.57 (m, 2 H), 1.37 (ddd, $J=13.0, 10.4, 2.7$ Hz, 1 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 140.1, 136.1, 71.3, 59.4, 35.5, 34.6, 29.5, 28.2, 28.0, 26.1, 18.3, 16.3, –4.1, –4.5 ppm; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{31}\text{O}_2\text{Si}^+ [M-\text{H}]^+$ 283.2088, found 283.2095.



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[(1*R*)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(*tert*-butyl)di-methylsilane [(*R*)-8]: Following the reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014), chiral allylic bromide (**(*R*)-8**) was prepared. To a solution of chiral OTBS ether alcohol (**(*R*)-S-9**) (2.39 g, 8.40 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) was added triethylamine (2.33 mL, 17 mmol, 2.0 equiv). The solution was cooled to -50°C , and methanesulfonyl chloride (1.10 mL, 14.0 mmol, 1.7 equiv) was added dropwise. The solution was stirred at this temperature for 1 h, during which a thick white suspension was formed. A solution of lithium bromide (2.56 g, 2.90 mmol, 3.5 equiv) in THF (10 mL) was then transferred to the reaction flask via cannula over 10 min. The mixture was allowed to warm to -20°C and was stirred at this temperature for 1 h. The reaction was quenched by pouring the slurry into water (100 mL). The resulting mixture was extracted with hexanes (100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give the chiral allylic bromide (**(*R*)-8**) (2.90 g, 8.40 mmol, quant. yield) as a colorless oil. This material was essentially pure, could be stored neat at -40°C for several months with no signs of decomposition, and could be used directly in further reactions. (**(*R*)-8**): $R_f=0.80$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = -75.9$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2955, 2929, 2856, 1471, 1463, 1387, 1362, 1352, 1250, 1204, 1147, 1139, 1122, 1082, 1050, 1026, 1005, 979, 936, 887, 833, 813, 771, 709, 678 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.05 (d, $J=10.2$ Hz, 1 H), 4.02 (ap t, $J=6.6$ Hz, 1 H), 3.95 (d, $J=10.2$ Hz, 1 H), 1.83–1.76 (m, 4 H), 1.65–1.54 (m, 2 H), 1.42 (m, 1 H), 1.12 (s, 3 H), 1.09 (s, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.7, 136.3, 71.5, 35.9, 35.3, 30.3, 29.3, 28.6, 28.1, 26.0, 18.3, 16.6, –4.0, –4.6 ppm; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{30}\text{BrOSi}^+ [M-\text{H}]^+$ 345.1244, found 345.1257.

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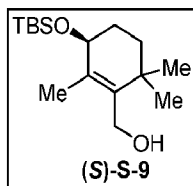


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Methyl (3*S*)-3-hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxylate [(*S*)-S-8]: According to the procedure for the preparation of (**(*R*)-S-8**) as described above, enone **S-7** (1.00 g, 5.00 mmol, 1.0 equiv) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (139 mg, 500 μmol , 0.1 equiv) were reacted to give product (**(*S*)-S-8**) [939 mg, 4.75 mmol, 95%, 96% ee, (determined by ^1H NMR spectroscopic analysis of its mosher ester)] as a colorless oil. (**(*S*)-S-8**): $R_f=0.50$ (silica gel, EtOAc:hexanes 1:2); $[\alpha]_D^{22} = -55.8$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3402, 3940, 2868, 1723, 1654, 1452, 1433, 1385, 1385, 1364, 1344, 1293, 1244, 1223, 1207, 1175, 1138, 1064, 1038, 1019, 1001, 968, 940, 901, 876, 860, 818, 778, 752, 660 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 3.98 (ap t,

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$J=5.1$ Hz, 1 H), 3.75 (s, 3 H), 1.96 (dddd, $J=13.8, 10.5, 5.2, 3.2$ Hz, 1 H), 1.76 (s, 1 H), 1.73 (ddd, $J=11.1, 5.3, 2.7$ Hz, 1 H), 1.60 (ddd, $J=13.4, 10.5, 3.1$ Hz, 2 H), 1.45 (ddd, $J=13.4, 8.0, 3.2$ Hz, 1 H), 1.10 (s, 3 H), 1.08 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 170.7, 138.5, 134.0, 68.9, 51.4, 34.4, 33.8, 28.6, 28.4, 27.5, 18.1 ppm; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3\text{Na}^+$ $[M+\text{Na}]^+$ 221.1148, found 221.1147.

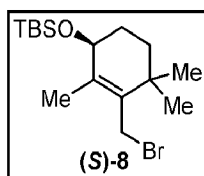


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[(3S)-3-[(*tert*-Butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methanol [(S)-S-9]:

According to the same procedure for the preparation of (*R*)-S-9 as described above, (*S*)-S-8 (793 mg, 4.00 mmol, 1.0 equiv) was treated with TBSCl (965 mg, 6.40 mmol, 1.6 equiv) to form the OTBS ether, followed by DIBAL-H (10.8 mL, 1.0 M solution in hexanes, 10.8 mmol, 2.7 equiv) to generate the primary alcohol from the ester moiety, to give product (*S*)-S-9 (1.06 g, 3.64 mmol, 91% for two steps) as a colorless oil. (*S*)-S-9: $R_f=0.20$ (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22}=+18.5$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3451, 2953, 2929, 2857, 1472, 1462, 1361, 1253, 1084, 1061, 1033, 1005, 985, 933, 886, 834, 815, 773, 669 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.14 (d, $J=11.4$ Hz, 1 H), 4.09 (d, $J=11.4$ Hz, 1 H), 4.00 (ap t, $J=5.8$ Hz, 1 H), 1.87–1.74 (m, 4 H), 1.65–1.57 (m, 2 H), 1.37 (ddd, $J=13.0, 10.4, 2.7$ Hz, 1 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 140.1, 136.1, 71.3, 59.4, 35.5, 34.6, 29.5, 28.2, 28.0, 26.1, 18.3, 16.3, –4.1, –4.5 ppm; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{31}\text{O}_2\text{Si}^+$ $[M-\text{H}]^+$ 283.2088, found 283.2095.

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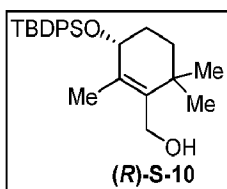


{[(1R)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(*tert*-butyl)di-methylsilane [(S)-8]:

According to the procedure for the preparation of (*R*)-8 as described above, (*S*)-S-9 (797 mg, 2.80 mmol, 1.0 equiv) was treated with MsCl (368 μL , 545 mg, 4.76 mmol, 1.7 equiv), followed by LiBr (851 mg, 9.80 mmol, 3.5 equiv), to give chiral allylic bromide (*S*)-8 (972 mg, 2.80 mmol, quant. yield) as colorless oil. The material was analytically pure and could be stored neat at -40°C for several months with no signs of decomposition. (*S*)-8: $R_f=0.80$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22}=+77.8$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2955, 2929, 2856, 1471, 1463, 1387, 1362, 1352, 1251, 1204, 1147, 1139, 1122, 1082, 1051, 1026, 1005, 936, 887, 833, 813, 771, 730, 709, 678 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.05 (d, $J=10.2$ Hz, 1 H), 4.02 (ap t, $J=6.6$ Hz, 1 H), 3.95 (d, $J=10.2$ Hz, 1 H), 1.83–1.76 (m, 4 H), 1.65–1.54 (m, 2 H), 1.41 (ddd, $J=13.4, 10.9, 2.5$ Hz, 1 H), 1.12 (s, 3 H), 1.09 (s, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.7, 136.3, 71.5, 35.9, 35.3, 30.3, 29.3, 28.6, 28.1, 26.0, 18.3, 16.6, –4.0, –4.6 ppm; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{30}\text{BrOSi}^+$ $[M-\text{H}]^+$ 345.1244, found 345.1258.

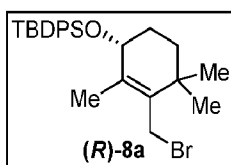
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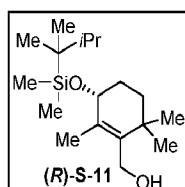
[(3R)-3-[(*tert*-Butyl(diphenyl)silyl]oxy)-2,6,6-trimethylcyclohex-1-en-1-yl]-

methanol [(R)-S-10]: According to the procedure for the preparation of (R)-S-9 as described above, allylic alcohol (R)-S-8 (397 mg, 2.00 mmol, 1.0 equiv) was treated with *tert*-butyldiphenylsilyl chloride (480 mg, 3.20 mmol, 1.6 equiv), followed by DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) to give product (R)-S-10 (740 mg, 1.80 mmol, 90% yield for two steps) as a colorless oil that slowly solidified to form an amorphous solid. (R)-S-10: R_f =0.30 (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22}$ = +9.6 (c = 1.0, CH₂Cl₂); FT-IR (neat) ν_{max} : 3452, 2958, 2930, 2857, 1472, 1427, 1388, 1363, 1352, 1200, 1146, 1105, 1081, 1049, 1026, 1003, 978, 936, 882, 821, 786, 738, 700, 668 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.75–7.67 (m, 4H), 7.46–7.34 (m, 6H), 4.12 (dd, J =11.3, 4.5 Hz, 1H), 4.08 (dd, J =11.3, 4.1 Hz, 1H), 4.02 (ap t, J =5.3 Hz, 1H), 1.74 (s, 3H), 1.68–1.61 (m, 2H), 1.60–1.53 (m, 1H), 1.26–1.21 (m, 1H), 1.07 (s, 3H), 1.06 (s, 9H), 0.94 (s, 3H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 140.5, 136.2, 135.7, 134.9, 134.3, 129.7, 129.6, 127.7, 127.5, 72.4, 59.3, 35.2, 34.6, 29.0, 28.2, 27.8, 27.3, 19.7, 16.9 ppm; HRMS (CI) calcd for C₂₆H₃₅O₂Si⁺ [M -H]⁺ 407.2401, found 407.2410.



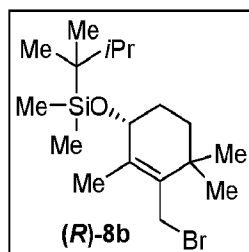
{[(1R)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(*tert*-butyl)diphenylsilane [(R)-

8a]: According to the procedure for the preparation of (R)-8 as described above, (R)-S-10 (613 mg, 1.50 mmol, 1.0 equiv) was reacted sequentially with MsCl (197 μ L, 292 mg, 2.55 mmol, 1.7 equiv) and LiBr (457 mg, 5.25 mmol, 3.5 equiv) to give chiral allylic bromide (R)-8a (707 mg, 1.50 mmol, quant. yield) as colorless oil. The material was essentially pure and could be stored neat at -40 °C for several months with no signs of decomposition. (R)-8a: R_f =0.75 (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22}$ = +26.2 (c =1.0, CH₂Cl₂); FT-IR (neat) ν_{max} : 2957, 2931, 2856, 1471, 1427, 1388, 1362, 1350, 1202, 1146, 1105, 1080, 1048, 1026, 1005, 979, 936, 883, 821, 787, 739, 700, 668 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.73–7.69 (m, 4H), 7.45–7.36 (m, 6H), 4.05–4.00 (m, 2H), 3.97 (d, J =10.1 Hz, 1H), 1.72 (s, 3H), 1.68–1.62 (m, 2H), 1.59–1.56 (m, 1H), 1.28–1.26 (m, 1H), 1.13 (s, 3H), 1.06 (s, 9H), 1.04 (s, 3H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 139.1, 136.9, 136.2, 134.7, 134.1, 129.73, 129.66, 127.7, 127.6, 72.3, 35.32, 35.28, 30.1, 28.6, 28.5, 28.0, 27.2, 19.7, 17.4 ppm; HRMS (CI) calcd for C₂₆H₃₄BrOSi⁺ [M -H]⁺ 469.1557, found 469.1550.



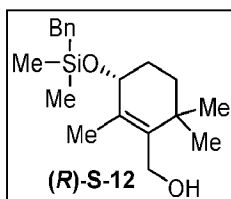
[(3*R*)-3-[(2,3-Dimethylbutan-2-yl)(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methanol [(*R*)-S-11**]:**

According to the procedure for the preparation of (*R*)-**S-9** as described above, allylic alcohol (*R*)-**S-8** (397 mg, 2.00 mmol, 1.0 equiv) was reacted sequentially with hexyldimethylsilyl chloride (572 mg, 3.20 mmol, 1.6 equiv) and DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) to give product (*R*)-**S-11** (560 mg, 1.78 mmol, 89% for two steps) as a colorless oil. (*R*)-**S-11**: R_f =0.20 (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = -13.8$ ($c=1.0$, CH₂Cl₂); FT-IR (neat) $\nu_{\max}$: 3455, 2956, 2867, 1467, 1388, 1376, 1364, 1352, 1251, 1203, 1148, 1138, 1120, 1080, 1051, 1034, 1025, 1007, 979, 936, 886, 876, 840, 828, 772, 707, 678 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.10 (ABq, $\Delta\delta_{AB}=0.040$, $J=11.4$ Hz, 2 H), 3.96 (ap t, $J=5.5$ Hz, 1 H), 1.84–1.73 (m, 4 H), 1.68–1.57 (m, 3 H), 1.35 (ddd, $J=12.3$, 9.7, 2.6 Hz, 1 H), 1.05 (s, 3 H), 1.00 (s, 3 H), 0.87 (dd, $J=6.9$, 1.6 Hz, 6 H), 0.84 (d, $J=3.0$ Hz, 6 H), 0.12 (d, $J=5.8$ Hz, 6 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 141.9, 138.0, 73.0, 61.2, 37.4, 36.6, 36.2, 31.4, 30.1, 30.0, 27.0, 22.5, 22.4, 20.8, 20.7, 18.4, 0.0, -0.6 ppm; HRMS (CI) calcd for C₁₈H₃₅O₂Si⁺ [*M*-H]⁺ 311.2401, found 311.2400.



[(1*R*)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy(2,3-dimethylbutan-2-yl)dimethylsilane [(*R*)-8b**]:**

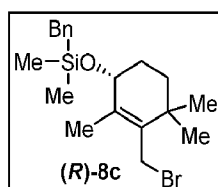
According to the procedure for the preparation of (*R*)-**8** as described above, (*R*)-**S-11** (469 mg, 1.50 mmol, 1.0 equiv) was reacted sequentially with MsCl (197 μ L, 292 mg, 2.55 mmol, 1.7 equiv) and LiBr (457 mg, 5.25 mmol, 3.5 equiv) to give chiral allylic bromide (*R*)-**8b** (563 mg, 1.50 mmol, quant. yield) as colorless oil. The material was essentially pure and could be stored neat at -40 °C for several months with no signs of decomposition. (*R*)-**8b**: R_f =0.80 (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = -45.9$ ($c=1.0$, CH₂Cl₂); FT-IR (neat) $\nu_{\max}$: 2956, 2866, 1467, 1389, 1377, 1364, 1352, 1250, 1203, 1147, 1138, 1121, 1081, 1050, 1033, 1026, 1008, 979, 936, 885, 875, 840, 827, 772, 708, 677 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.10–3.93 (m, 3 H), 1.84–1.73 (m, 4 H), 1.68–1.57 (m, 3 H), 1.43–1.36 (m, 1 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 0.89 (d, $J=1.6$ Hz, 3 H), 0.88 (d, $J=1.6$ Hz, 3 H), 0.851 (s, 3 H), 0.845 (s, 3 H), 0.13 (s, 3 H), 0.12 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 139.6, 136.2, 71.2, 35.7, 35.3, 34.3, 30.3, 29.1, 28.4, 28.3, 20.5, 20.4, 18.8, 18.7, 16.8, -1.9, -2.6 ppm; HRMS (CI) calcd for C₁₈H₃₄BrOSi⁺ [*M*-H]⁺ 373.1557, found 373.1556.



[(3*R*)-3-[(Benzyl(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methanol [(*R*)-S-12**]:**

According to the procedure for the preparation of (*R*)-**S-9** as described above, allylic alcohol (*R*)-**S-8** (397 mg, 2.00 mmol, 1.0 equiv) was sequentially reacted with benzyldimethylsilyl chloride (547 mg, 3.20 mmol,

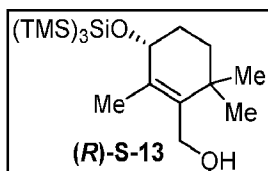
1.6 equiv) and DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) to give product **(R)-S-12** (586 mg, 1.84 mmol, 92% for two steps) as a colorless oil. **(R)-S-12**: $R_f=0.25$ (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = +5.8$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3456, 2957, 2937, 2865, 1600, 1493, 1470, 1452, 1406, 1388, 1364, 1353, 1251, 1207, 1154, 1121, 1079, 1055, 1028, 981, 936, 904, 889, 835, 817, 796, 762, 698 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.25–7.18 (m, 2H), 7.12–7.05 (m, 3H), 4.15 (d, $J=10.6$ Hz, 1H), 4.10 (d, $J=11.3$ Hz, 1H), 4.02 (ap t, $J=5.6$ Hz, 1H), 2.22 (s, 2H), 1.80–1.75 (m, 1H), 1.77 (s, 3H), 1.65–1.57 (m, 2H), 1.35 (ddd, $J=13.5$, 9.9, 2.8 Hz, 1H), 1.08 (s, 3H), 1.02 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 140.8, 139.2, 135.2, 128.6, 128.3, 124.3, 71.4, 59.3, 35.3, 34.6, 29.4, 28.0, 27.5, 16.3, –1.49, –1.52 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{29}\text{O}_2\text{Si}^+ [M-\text{H}]^+$ 317.1931, found 317.1942.



Benzyl[(1R)-3-(bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxydimethylsilane [(R)-8c]:

According to the procedure for the preparation of **(R)-8** as described above, **(R)-S-12** (478 mg, 1.50 mmol, 1.0 equiv) was reacted sequentially with MsCl (197 μL , 292 mg, 2.55 mmol, 1.7 equiv) and LiBr (457 mg, 5.25 mmol, 3.5 equiv) to give chiral allylic bromide **(R)-8c** (574 mg, 1.50 mmol, quant. yield) as colorless oil.

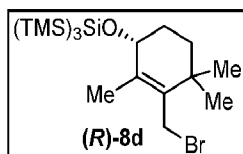
The material was essentially pure and could be stored neat at -40°C for several months with no signs of decomposition. **(R)-8c**: $R_f=0.75$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = +10.7$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2957, 2936, 2866, 1600, 1493, 1470, 1451, 1406, 1387, 1364, 1353, 1251, 1206, 1153, 1121, 1079, 1054, 1028, 980, 936, 904, 889, 836, 817, 795, 761, 698 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.24–7.19 (m, 2H), 7.09–7.04 (m, 3H), 4.07–4.00 (m, 2H), 4.10 (d, $J=10.1$ Hz, 1H), 2.22 (s, 2H), 1.80–1.75 (m, 1H), 1.74 (s, 3H), 1.62–1.55 (m, 2H), 1.42–1.38 (m, 1H), 1.12 (s, 3H), 1.11 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.2, 138.8, 137.0, 128.6, 128.3, 124.3, 71.6, 35.7, 35.3, 30.0, 29.2, 28.4, 28.1, 27.5, 16.5, –1.46, –1.53 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{28}\text{BrOSi}^+ [M-\text{H}]^+$ 379.1087, found 379.1090.



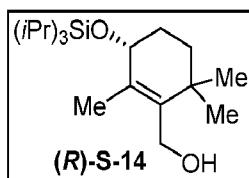
[(3R)-3-[[1,1,3,3,3-Hexamethyl-2-(trimethylsilyl)trisilan-2-yl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methanol [(R)-S-13]:

According to a similar procedure for the preparation of **(R)-S-9** as described above, allylic alcohol **(R)-S-8** (397 mg, 2.00 mmol, 1.0 equiv) was reacted with tris(trimethylsilyl)silyl chloride (905 mg, 3.20 mmol, 1.6 equiv) and N,N -dimethylpyridin-4-amine (DMAP; 390 mg, 3.20 mmol, 1.6 equiv) as base, followed by DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) reduction, to give product **(R)-S-13** (710 mg, 1.70 mmol, 85% for two steps) as a colorless oil. **(R)-S-13**: $R_f=0.30$ (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = -10.2$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3451, 2948, 2894, 1728, 1470, 1438,

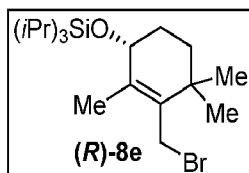
- 1395, 1364, 1346, 1256, 1243, 1203, 1146, 1121, 1077, 1041, 1004, 971, 933, 864, 827, 792, 768, 743, 685, 664 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.10 (ABq, $\Delta\delta_{\text{AB}}=0.032$, $J=11.4$ Hz, 2H), 3.70 (ap t, $J=5.4$ Hz, 1H), 1.85–1.74 (m, 4H), 1.66–1.54 (m, 2H), 1.32 (ddd, $J=13.2$, 9.5, 2.8 Hz, 1H), 1.05 (s, 3H), 1.00 (s, 3H), 0.20 (s, 27H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.7, 136.0, 75.4, 59.2, 35.2, 34.7, 28.8, 28.1, 27.8, 16.6, 0.8 ppm;
- 5 HRMS (CI) calcd for $\text{C}_{19}\text{H}_{43}\text{O}_2\text{Si}_4^+ [M-H]^+$ 415.2335, found 415.2345.



- 2-[[**(1R)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl**oxy]-1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane [**(R)-8d**]: According to the procedure for the preparation of **(R)-8** as described above, **(R)-S-13** (625 mg, 1.50 mmol, 1.0 equiv) was reacted sequentially with MsCl (197 μL , 292 mg, 2.55 mmol, 1.7 equiv) and LiBr (457 mg, 5.25 mmol, 3.5 equiv) to give chiral allylic bromide **(R)-8d** (720 mg, 1.50 mmol, quant. yield) as colorless oil. The material was essentially pure and could be stored neat at -40°C for several months with no signs of decomposition. **(R)-8d**: $R_f=0.85$ (silica gel, EtOAc :hexanes 1:10); $[\alpha]_{\text{D}}^{22}=-27.0$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2948, 2894, 1728, 1470, 1438, 1395, 1364, 1346, 1256, 1243, 1203, 1146, 1121, 1077, 1041, 1004, 971, 933, 864, 827, 792, 768, 743, 685, 664 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.03 (d, $J=10.1$ Hz, 1H), 3.95 (d, $J=10.1$ Hz, 1H), 3.71 (ap t, $J=5.7$ Hz, 1H), 1.84–1.72 (m, 4H), 1.59–1.53 (m, 2H), 1.38–1.31 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 0.20 (s, 27H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.7, 136.0, 75.5, 35.5, 35.4, 30.1, 28.6, 28.3, 28.2, 16.9, 0.8 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{42}\text{BrOSi}_4^+ [M-H]^+$ 477.1502, found 477.1501.
- 15

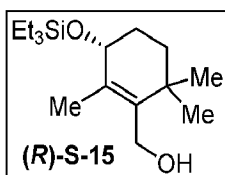


- 20 **[(3R)-2,6,6-Trimethyl-3-[(triisopropylsilyl)oxy]cyclohex-1-en-1-yl]methanol [(R)-S-14]:** According to the procedure for the preparation of **(R)-S-9** as described above, allylic alcohol **(R)-S-8** (397 mg, 2.00 mmol, 1.0 equiv) was reacted sequentially with triisopropylsilyl chloride (686 μL , 617 mg, 3.20 mmol, 1.6 equiv) and DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) to give product **(R)-S-14** (575 mg, 1.76 mmol, 88% for two steps) as a colorless oil. **(R)-S-14**: $R_f=0.28$ (silica gel, EtOAc :hexanes 1:9); $[\alpha]_{\text{D}}^{22}=-17.3$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3445, 2943 2890 2864 1464, 1385 1364, 1348, 1245, 1218, 1203, 1178, 1148, 1139, 1122, 1088, 1053, 1027, 1012, 997, 982, 935, 921, 903, 882, 813, 779, 731, 708, 676 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.17 (ap t, $J=5.5$ Hz, 1H), 4.11 (ABq, $\Delta\delta_{\text{AB}}=0.042$, $J=11.4$ Hz, 2H), 1.93–1.77 (m, 1H), 1.85 (s, 3H), 1.72–1.58 (m, 2H), 1.39–1.32 (m, 1H), 1.26–1.03 (m, 3H), 1.09 (s, 9H), 1.08 (s, 9H), 1.06 (s, 3H), 1.01 (s, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.8, 136.3, 71.6, 59.3, 35.5, 34.6, 29.6, 28.1, 28.0, 18.5, 18.4, 16.5, 13.0 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{37}\text{O}_2\text{Si}^+ [M-H]^+$ 325.2557, found 325.2556.
- 25
- 30

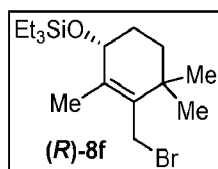


{[(1R)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(triisopropyl)silane [(R)-8e]:

According to the procedure for the preparation of (R)-8 as described above, (R)-S-14 (490 mg, 1.50 mmol, 1.0 equiv) was reacted sequentially with MsCl (197 μ L, 292 mg, 2.55 mmol, 1.7 equiv) and LiBr (457 mg, 5.25 mmol, 3.5 equiv) to give chiral allylic bromide (R)-8e (584 mg, 1.50 mmol, quant. yield) as colorless oil. The material was essentially pure and could be stored neat at -40°C for several months with no signs of decomposition. (R)-8e: $R_f=0.90$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = -55.5$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2942, 2892, 2865, 1464, 1384, 1364, 1348, 1244, 1217, 1203, 1177, 1147, 1139, 1122, 1088, 1052, 1027, 1011, 996, 980, 935, 920, 903, 881, 811, 779, 730, 706, 675 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.18 (ap t, $J=5.9\text{ Hz}$, 1 H), 4.01 (ABq, $\Delta\delta_{\text{AB}}=0.081$, $J=11.4\text{ Hz}$, 2 H), 1.88–1.81 (m, 1 H), 1.84 (s, 3 H), 1.72–1.58 (m, 2 H), 1.40 (ddd, $J=13.1$, 10.3, 2.8 Hz, 1 H), 1.15–1.03 (m, 3 H), 1.11 (s, 3 H), 1.10 (s, 3 H), 1.092 (s, 9 H), 1.087 (s, 9 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.9, 136.2, 71.8, 35.8, 35.3, 30.4, 29.3, 28.4, 28.3, 18.5, 18.4, 16.8, 13.0 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{36}\text{BrOSi}^+ [M-\text{H}]^+$ 387.1713, found 387.1714.



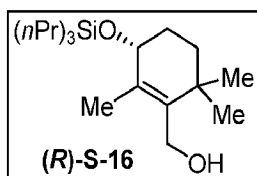
{(3R)-2,6,6-Trimethyl-3-[(triethylsilyl)oxy]cyclohex-1-en-1-yl}methanol [(R)-S-15]: According to the procedure for the preparation of (R)-S-9 as described above, allylic alcohol (R)-S-8 (397 mg, 2.00 mmol, 1.0 equiv) was reacted sequentially with triethylsilyl chloride (537 μ L, 482 mg, 3.20 mmol, 1.6 equiv) and DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) to give product (R)-S-15 (512 mg, 1.80 mmol, 90% for two steps) as a colorless oil. (R)-S-15: $R_f=0.35$ (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = -8.5$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3453, 2954, 2938, 2911, 2876, 1468, 1457, 1415, 1364, 1351, 1237, 1203, 1148, 1139, 1122, 1084, 1053, 1006, 978, 936, 883, 823, 792, 741, 726, 686 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.07 (ABq, $\Delta\delta_{\text{AB}}=0.043$, $J=10.9\text{ Hz}$, 2 H), 3.99 (ap t, $J=5.6\text{ Hz}$, 1 H), 1.88–1.75 (m, 1 H), 1.78 (s, 3 H), 1.65–1.54 (m, 2 H), 1.34 (ap t, $J=11.2\text{ Hz}$, 1 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 0.95 (t, $J=8.0\text{ Hz}$, 9 H), 0.61 (q, $J=7.8\text{ Hz}$, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 140.2, 135.6, 71.1, 59.1, 35.4, 34.5, 29.5, 28.0, 27.8, 16.1, 7.0, 5.2 ppm; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{31}\text{O}_2\text{Si}^+ [M-\text{H}]^+$ 283.2088, found 283.2090.



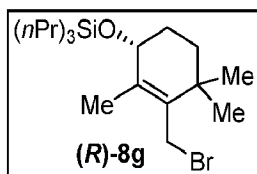
{[(1*R*)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(triethyl)silane [(*R*)-8f]:

According to the same procedure for the preparation of (*R*)-8 described above, (*R*)-S-15 (427 mg, 1.50 mmol, 1.0equiv) was reacted sequentially with MsCl (197 μ L, 292 mg, 2.55 mmol, 1.7equiv) and LiBr (457 mg, 5.25 mmol, 3.5equiv) to give chiral allylic bromide (*R*)-8f (521 mg, 1.50 mmol, quant. yield) as colorless oil.

- 5 The material was essentially pure and could be stored neat at -40°C for several months with no signs of decomposition. (*R*)-8f: $R_f=0.85$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = -26.5$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2954, 2937, 2912, 2875, 1468, 1457, 1414, 1364, 1351, 1236, 1203, 1147, 1139, 1122, 1083, 1053, 1005, 978, 936, 882, 822, 791, 740, 725, 686 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.04 (ap t, $J=6.9$ Hz, 1 H), 4.00 (ABq, $\Delta\delta_{\text{AB}}=0.11$, $J=10.1$ Hz, 2 H), 1.85–1.78 (m, 1 H), 1.85–1.78 (s, 3 H), 1.68–1.57 (m, 2 H), 1.41 (ddd, $J=1j3.5$, 10.9, 2.8 Hz, 1 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 0.98 (t, $J=7.9$ Hz, 9 H), 0.64 (q, $J=7.9$ Hz, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.5, 136.6, 71.4, 35.9, 35.3, 30.2, 29.4, 28.5, 28.1, 16.4, 7.1, 5.2 ppm; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{30}\text{BrOSi}^+$ $[M-H]^+$ 345.1244, found 345.1252.



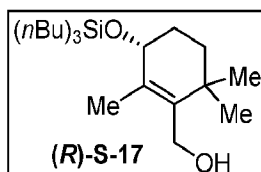
- 15 **{(3*R*)-2,6,6-Trimethyl-3-[(tripropylsilyl)oxy]cyclohex-1-en-1-yl)methanol [(*R*)-S-16]:** According to the procedure for the preparation of (*R*)-S-9 as described above, allylic alcohol (*R*)-S-8 (397 mg, 2.00 mmol, 1.0equiv) was reacted sequentially with tripropylsilyl chloride (686 μ L, 617 mg, 3.20 mmol, 1.6equiv) and DIBAL-H (5.40 mL, 1.0M solution in hexanes, 5.40 mmol, 2.7equiv) to give product (*R*)-S-16 (600 mg, 1.84 mmol, 92% for two steps) as a colorless oil. (*R*)-S-16: $R_f=0.40$ (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = -8.1$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3452, 2954, 2925, 2868, 1454, 1408, 1374, 1364, 1352, 1332, 1204, 1148, 1139, 1123, 1084, 1053, 1028, 1005, 981, 935, 894, 884, 831, 819, 754, 739, 713, 695 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.14 (dd, $J=11.4$, 3.8 Hz, 1 H), 4.09 (dd, $J=11.4$, 3.7 Hz, 1 H), 4.01 (ap t, $J=5.9$ Hz, 1 H), 1.84–1.74 (m, 1 H), 1.80 (s, 3 H), 1.65–1.58 (m, 2 H), 1.45–1.32 (m, 7 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.97 (t, $J=7.2$ Hz, 9 H), 0.70–0.55 (m, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 140.3, 135.9, 71.2, 59.3, 35.5, 34.6, 29.6, 28.2, 27.9, 18.7, 17.3, 17.1, 16.1 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{37}\text{O}_2\text{Si}^+$ $[M-H]^+$ 325.2557, found 325.2566.



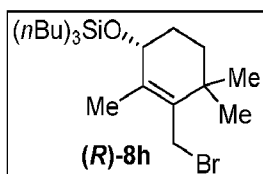
{[(1*R*)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(tripropyl)silane [(*R*)-8g]:

- According to the procedure for the preparation of (*R*)-8 as described above, (*R*)-S-16 (490 mg, 1.50 mmol, 1.0equiv) was reacted sequentially with MsCl (197 μ L, 292 mg, 2.55 mmol, 1.7equiv) and LiBr (457 mg, 5.25 mmol, 3.5equiv) to give chiral allylic bromide (*R*)-8g (584 mg, 1.50 mmol, quant. yield) as colorless oil. The material was essentially pure and could be stored neat at -40°C for several months with no signs of

decomposition. **(R)-8g**: $R_f=0.75$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = -24.5$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2954, 2924, 2867, 1454, 1407, 1374, 1364, 1351, 1333, 1203, 1148, 1139, 1122, 1084, 1052, 1028, 1006, 980, 935, 894, 883, 830, 818, 752, 739, 711, 697 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.05 (d, $J=10.2$ Hz, 1 H), 4.03 (ap t, $J=6.5$ Hz, 1 H), 3.94 (d, $J=10.1$ Hz, 1 H), 1.83–1.75 (m, 1 H), 1.78 (s, 3 H), 1.62–1.56 (m, 2 H), 1.42–1.35 (m, 7 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 0.97 (t, $J=7.2$ Hz, 9 H), 0.66–0.59 (m, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.6, 136.5, 71.4, 35.9, 35.3, 30.2, 29.4, 28.6, 28.1, 18.7, 17.3, 17.1, 16.4 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{36}\text{BrOSi}^+ [M-\text{H}]^+ 387.1713$, found 387.1726.



{(3R)-2,6,6-Trimethyl-3-[(tributylsilyl)oxy]cyclohex-1-en-1-yl)methanol [(R)-S-17]: According to the procedure for the preparation of **(R)-S-9** as described above, allylic alcohol **(R)-S-8** (397 mg, 2.00 mmol, 1.0 equiv) was reacted sequentially with tributylsilyl chloride (855 μL , 751 mg, 3.20 mmol, 1.6 equiv) and DIBAL-H (5.40 mL, 1.0 M solution in hexanes, 5.40 mmol, 2.7 equiv) to give product **(R)-S-17** (634 mg, 1.72 mmol, 86% for two steps) as a colorless oil. **(R)-S-17**: $R_f=0.45$ (silica gel, EtOAc:hexanes 1:9); $[\alpha]_D^{22} = -8.1$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 3455, 2956, 2922, 2873, 2855, 1465, 1409, 1375, 1365, 1351, 1342, 1296, 1252, 1198, 1139, 1148, 1139, 1123, 1079, 1052, 1028, 1007, 979, 964, 936, 888, 822, 789, 761, 733, 711, 695 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.12 (ABq, $\Delta\delta_{\text{AB}}=0.048$, $J=11.4$ Hz, 2 H), 4.02 (ap t, $J=5.8$ Hz, 1 H), 1.89–1.76 (m, 1 H), 1.80 (s, 3 H), 1.65–1.55 (m, 2 H), 1.39–1.36 (m, 1 H), 1.36–1.29 (m, 12 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.92–0.86 (m, 9 H), 0.66–0.60 (m, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 140.3, 135.9, 71.2, 59.4, 35.5, 34.6, 29.6, 28.2, 27.9, 26.9, 25.7, 16.2, 14.2, 13.9 ppm; HRMS (CI) calcd for $\text{C}_{22}\text{H}_{43}\text{O}_2\text{Si}^+ [M-\text{H}]^+ 367.3027$, found 367.3036.

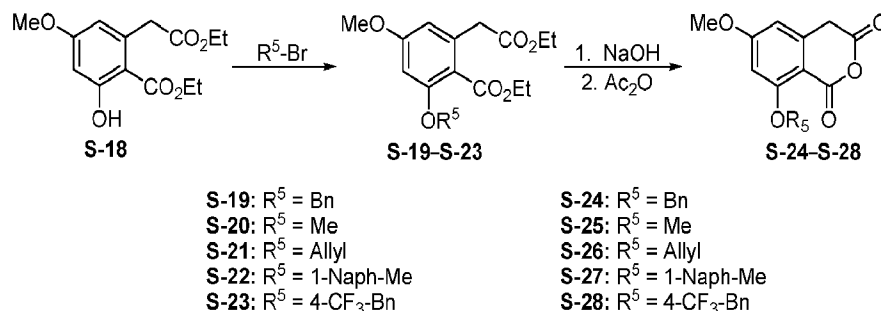


{[(1R)-3-(Bromomethyl)-2,4,4-trimethylcyclohex-2-en-1-yl]oxy}(tributyl)silane [(R)-8h]

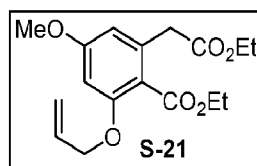
According to the procedure for the preparation of **(R)-8** as described above, **(R)-S-17** (552 mg, 1.50 mmol, 1.0 equiv) was reacted sequentially with MsCl (197 μL , 292 mg, 2.55 mmol, 1.7 equiv) and LiBr (457 mg, 5.25 mmol, 3.5 equiv) to give chiral allylic bromide **(R)-8h** (647 mg, 1.50 mmol, quant. yield) as colorless oil. The material was essentially pure and could be stored neat at -40°C for several months with no signs of decomposition. **(R)-8h**: $R_f=0.70$ (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{22} = -18.1$ ($c=1.0$, CH_2Cl_2); FT-IR (neat) ν_{max} : 2956, 2921, 2871, 2856, 1465, 1409, 1376, 1364, 1351, 1341, 1296, 1251, 1198, 1139, 1147, 1139, 1122, 1079, 1050, 1027, 1006, 979, 963, 935, 887, 821, 789, 760, 731, 712, 694 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 4.03 (ap t, $J=7.0$ Hz, 1 H), 4.00 (ABq, $\Delta\delta_{\text{AB}}=0.11$, $J=10.1$ Hz, 2 H), 1.84–1.75 (m, 1 H), 1.78 (s, 3 H),

1.66–1.57 (m, 2H), 1.41 (ddd, $J=13.5, 11.0, 2.7$ Hz, 1H), 1.35–1.30 (m, 12H), 1.13 (s, 3H), 1.09 (s, 3H), 0.92–0.87 (m, 9H), 0.66–0.58 (m, 6H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 139.6 136.5, 71.4, 35.9, 35.3, 30.3, 29.4, 28.6, 28.1, 26.9, 25.7, 16.5, 14.2, 13.9 ppm; HRMS (CI) calcd for $\text{C}_{22}\text{H}_{42}\text{BrOSi}^+$ [$M\text{--H}$] $^+$ 429.2183, found 429.2194.

5 Anthrones Synthesis



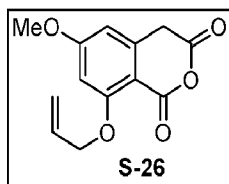
Compounds **S-18**, **S-19**, **S-20**, and cyclic anhydrides **S-24** and **S-25** were prepared following the reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). The physical and spectroscopic data of those compounds matched those reported in the literature (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014).



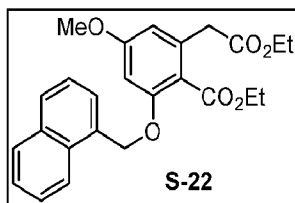
10

Ethyl 2-(allyloxy)-6-(2-ethoxy-2-oxoethyl)-4-methoxybenzoate (S-21): Following the reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014), **S-21** was synthesized as follows. To a solution of compound **S-18** (1.00 g, 3.50 mmol, 1.0 equiv) in DMF (25 mL) at 25 °C were sequentially added K_2CO_3 (1.00 g, 7.00 mmol, 2.0 equiv) and allyl bromide (364 μL , 3.85 mmol, 1.1 equiv). The reaction mixture was stirred for 15 h, then diluted with H_2O (25 mL) and extracted with EtOAc (3 $\times$ 50 mL). The organic phase was dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give a crude oil, which was purified by flash column chromatography (silica gel, 2% $\rightarrow$ 5% $\rightarrow$ 10% EtOAc:hexanes) to give pure product **S-21** (848 mg, 2.64 mmol, 75% yield) as a colorless oil. **S-21:** $R_f=0.30$ (silica gel, EtOAc:hexanes 1:4); FT-IR (neat) ν_{max} : 2981, 1727, 1603, 1583, 1459, 1443, 1388, 1374, 1332, 1266, 1192, 1153, 1116, 1086, 1053, 992, 933, 835, 772, 683 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.41–6.39 (m, 2H), 6.00 (ddd, $J=12.2, 10.6, 5.3$ Hz, 1H), 5.40 (ddd, $J=17.3, 3.1, 1.6$ Hz, 1H), 5.25 (dd, $J=10.6, 1.5$ Hz, 1H), 4.53 (ap dt, $J=4.9, 1.5$ Hz, 2H), 4.33 (q, $J=7.1$ Hz, 2H), 4.14 (q, $J=7.1$ Hz, 2H), 3.80 (s, 3H), 3.67 (s, 2H), 1.34 (t, $J=7.1$ Hz, 3H), 1.24 (t, $J=7.1$ Hz, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 170.9, 167.5, 161.6, 158.0, 135.2, 132.9, 117.5, 117.0, 107.9, 99.3, 69.7, 61.1, 61.0, 55.5, 39.7, 14.33, 14.28 ppm; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{23}\text{O}_6^+$ [$M\text{+H}$] $^+$ 323.1489, found 323.1494.

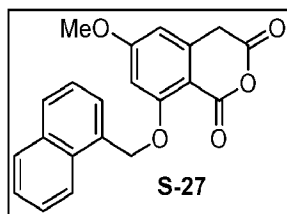
25



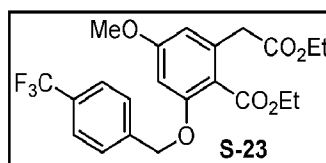
8-(Allyloxy)-6-methoxy-1H-isochromene-1,3(4H)-dione (S-26): Following the reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014), **S-26** was synthesized as follows. To a stirred solution of diester **S-21** (806 mg, 2.50 mmol, 1.0 equiv) in EtOH (10 mL) was added a solution of NaOH (2.70 g, 68.0 mmol, 27 equiv) in water (7 mL) at 25 °C. The resulting mixture was heated to reflux for 15 h. EtOH was then removed under reduced pressure, and the remaining aqueous phase was acidified with 12 N aq. HCl to pH 1. The aqueous phase was extracted with EtOAc (3×30 mL), and the combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude diacid as a white solid. To a stirred slurry of the so obtained diacid in toluene (6 mL) was added acetic anhydride (260 µL, 2.75 mmol, 1.1 equiv) via syringe, and the resulting mixture was heated to reflux for 1 h. The flask was then cooled in an ice bath, the solid product was filtered off, and the filter cake was washed with pentane. The solids were collected and dried to afford **S-26** as light yellow crystals (546 mg, 2.2 mmol, 88% yield for two steps). **S-26**: R_f=0.25 (silica gel, EtOAc:hexanes 1:4); m.p. = 115–116 °C (toluene); FT-IR (film) ν_{max}: 1786, 1742, 1603, 1583, 1388, 1374, 1332, 1272, 1223, 1198, 1175, 1152, 992, 933, 835, 772, 683 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.42 (d, *J*=1.4 Hz, 1 H), 6.34 (s, 1 H), 6.05 (ddd, *J*=15.5, 10.1, 4.7 Hz, 1 H), 5.60 (dd, *J*=17.2, 1.0 Hz, 1 H), 5.34 (dd, *J*=10.6, 0.8 Hz, 1 H), 4.65 (d, *J*=4.6 Hz, 2 H), 3.97 (s, 2 H), 3.87 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 165.8, 165.4, 162.9, 156.7, 138.8, 131.7, 118.3, 104.3, 103.7, 99.6, 69.8, 56.0, 35.5 ppm; HRMS (ESI) calcd for C₁₃H₁₂O₅Na⁺ [*M*+Na]⁺ 271.0577, found 271.0580.



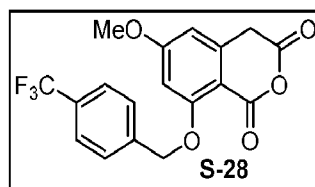
Ethyl 2-(2-ethoxy-2-oxoethyl)-4-methoxy-6-(1-naphthylmethoxy)benzoate (S-22): According to the procedure described above for the preparation of **S-21**, compound **S-18** (1.00 g, 3.50 mmol, 1.0 equiv) was reacted with 1-(bromomethyl)naphthalene (851 mg, 3.85 mmol, 1.1 equiv) to give product **S-22** (1.23 g, 2.90 mmol, 83% yield) as a colorless oil. **S-22**: R_f=0.20 (silica gel, EtOAc:hexanes 1:4); FT-IR (neat) ν_{max}: 2981, 1727, 1603, 1583, 1463, 1455, 1434, 1366, 1317, 1268, 1194, 1155, 1095, 1071, 1048, 1027, 1002, 961, 804, 776, 739, 678 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.03 (d, *J*=8.2 Hz, 1 H), 7.90–7.81 (m, 2 H), 7.61 (d, *J*=6.8 Hz, 1 H), 7.55–7.49 (m, 2 H), 7.45 (dd, *J*=8.1, 7.2 Hz, 1 H), 6.60 (d, *J*=2.2 Hz, 1 H), 6.46 (d, *J*=2.2 Hz, 1 H), 5.50 (s, 2 H), 4.19–4.11 (m, 4 H), 3.81 (s, 3 H), 3.70 (s, 2 H), 1.25 (t, *J*=7.1 Hz, 3 H), 1.05 (t, *J*=7.1 Hz, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 171.0, 167.5, 161.7, 158.2, 135.5, 133.8, 132.1, 131.4, 129.0, 128.8, 126.5, 126.3, 126.0, 125.4, 123.8, 117.2, 108.0, 99.5, 69.5, 61.06, 61.05, 55.6, 39.7, 14.3, 14.0 ppm; HRMS (ESI) calcd for C₂₅H₂₇O₆⁺ [*M*+H]⁺ 423.1802, found 423.1800.



6-Methoxy-8-(1-naphthylmethoxy)-1H-isochromene-1,3(4H)-dione (S-27): According to the procedure described above for the preparation of **S-26**, diester **S-22** (1.06 g, 2.50 mmol, 1.0 equiv) was reacted with NaOH (2.70 g, 68.0 mmol, 27 equiv) in water (7 mL), followed by Ac₂O (260 μ l, 2.75 mmol, 1.1 equiv) to afford product **S-27** as light yellow crystals (731 mg, 2.10 mmol, 84% yield for two steps). **S-27**: R_f=0.20 (silica gel, EtOAc:hexanes 1:4); m.p. = 191–192 °C (toluene); FT-IR (film) ν_{max} : 1780, 1733, 1609, 1585, 1350, 1334, 1273, 1224, 1196, 1177, 1148, 1002, 966, 802, 776, 739, 677 cm⁻¹; ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.21–8.16 (m, 1 H), 7.99–7.88 (m, 3 H), 7.55 (m, 3 H), 6.98 (s, 1 H), 6.59 (s, 1 H), 5.71 (s, 2 H), 4.17 (s, 2 H), 3.88 (s, 3 H) ppm; ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.2, 165.3, 161.9, 157.0, 140.6, 133.1, 132.0, 130.5, 128.4, 128.3, 126.3, 126.0, 125.5, 125.4, 123.8, 104.6, 103.0, 99.4, 68.5, 56.0, 35.0 ppm; HRMS (ESI) calcd for C₂₁H₁₇O₅⁺ [M+H]⁺ 349.1071, found 349.1074.



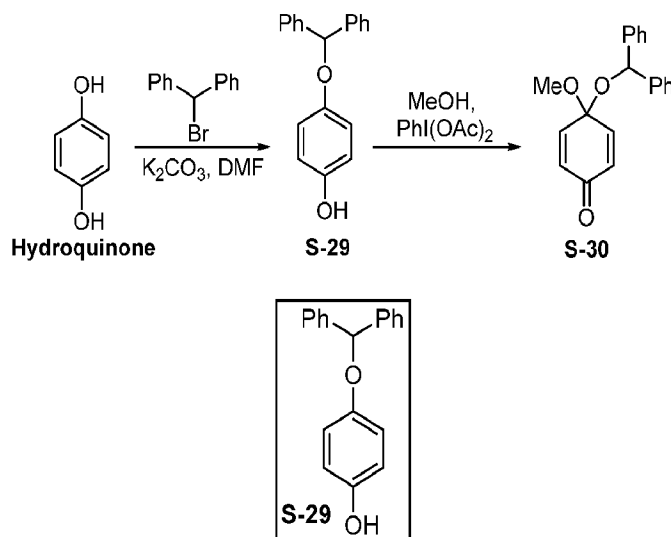
ethyl 2-(2-ethoxy-2-oxoethyl)-4-methoxy-6-[[4-(trifluoromethyl)benzyl]oxy]benzoate (S-23): According to the procedure described above for the preparation of **S-21**, compound **S-18** (1.00 g, 3.50 mmol, 1.0 equiv) was reacted with 1-(bromomethyl)-4-(trifluoromethyl)benzene (920 mg, 3.85 mmol, 1.1 equiv) to give product **S-23** (1.26 g, 2.86 mmol, 82% yield) as a colorless oil. **S-23**: R_f=0.30 (silica gel, EtOAc:hexanes 1:4); FT-IR (neat) ν_{max} : 2981, 1729, 1603, 1583, 1463, 1456, 1434, 1367, 1320, 1317, 1268, 1194, 1156, 1095, 1071, 1048, 1027, 961, 844, 834, 738, 698 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.62 (d, *J*=8.2 Hz, 2 H), 7.54 (d, *J*=8.0 Hz, 2 H), 6.45 (d, *J*=2.1 Hz, 1 H), 6.42 (d, *J*=2.1 Hz, 1 H), 5.13 (s, 2 H), 4.33 (q, *J*=7.1 Hz, 2 H), 4.15 (q, *J*=7.1 Hz, 2 H), 3.79 (s, 3 H), 3.70 (s, 2 H), 1.30 (t, *J*=7.1 Hz, 3 H), 1.25 (t, *J*=7.1 Hz, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 170.9, 167.3, 161.7, 157.7, 140.8, 135.6, 130.21 (q, *J*=32.5 Hz), 127.2, 125.58 (q, *J*=3.9 Hz), 124.22 (q, *J*=272.1 Hz), 117.1, 108.3, 99.4, 69.9, 61.2, 61.1, 55.6, 39.8, 14.29, 14.27 ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ -61.59 (s) ppm; HRMS (ESI) calcd for C₂₂H₂₄F₃O₆⁺ [M+H]⁺ 441.1519, found 441.1522.



6-Methoxy-8-[[4-(trifluoromethyl)benzyl]oxy]-1H-isochromene-1,3(4H)-dione (S-28): According to the procedure described above for the preparation of **S-26**, diester **S-23** (1.12 g, 2.50 mmol, 1.0 equiv) was reacted with NaOH (2.70 g, 68.0 mmol, 27 equiv) in water (7 mL), followed by Ac₂O (260 μ l, 2.75 mmol,

1.1 equiv) to afford product **S-28** as light yellow crystals (733 mg, 2.00 mmol, 80% yield for two steps). **S-28**: $R_f=0.30$ (silica gel, EtOAc:hexanes 1:4); m.p.=214–215 °C (toluene); FT-IR (film) $\nu_{\max}$: 1781, 1755, 1733, 1605, 1580, 1442, 1346, 1324, 1270, 1236, 1201, 1158, 1112, 1066, 1017, 981, 954, 922, 844, 832, 774, 684 cm^{-1} ; ^1H NMR (600 MHz, acetone- d_6) δ 7.89 (d, $J=7.8$ Hz, 2H), 7.77 (d, $J=7.8$ Hz, 2H), 6.77 (s, 1H), 6.67 (s, 1H), 5.44 (s, 2H), 4.20 (s, 2H), 3.93 (s, 3H) ppm; ^{13}C NMR (151 MHz, acetone- d_6) δ 166.7, 166.5, 163.0, 157.8, 142.4, 141.30, 141.25, 130.1 (q, $J=32.0$ Hz), 128.1, 126.2 (q, $J=3.9$ Hz), 125.4 (q, $J=271.2$ Hz), 105.7, 100.2, 70.3, 56.5, 35.8 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -61.63 (s) ppm; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{O}_5^+$ $[M+\text{Na}]^+$ 389.0607, found 389.0611.

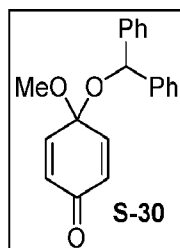
Scheme 3. Anthrone Semi-Quinone Fragment I3 Synthesis



4-(Diphenylmethoxy)phenol (S-29): Phenol **S-29** was synthesized according to the reported procedure (Frlan *et al.*, 2007). To a stirred suspension of hydroquinone (2.20 g, 20.0 mmol, 1.0 equiv) and K_2CO_3 (1.38 g, 10.0 mmol, 0.5 equiv) in acetone (20 mL) under argon was added (bromomethylene)dibenzene (2.47 g, 10.0 mmol, 0.5 equiv). The mixture was heated to reflux for 15 h, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 2%→5%→10% EtOAc:hexanes) furnished pure product **S-29** (1.94 g, 7.00 mmol, 70% yield) as a white solid. **S-29**: $R_f=0.50$ (silica gel, EtOAc:hexanes 1:9); m.p.=106–108 °C (CH_2Cl_2); FT-IR (film) $\nu_{\max}$: 3356, 3029, 2923, 1505, 1452, 1260, 1208, 1100, 1081, 1013, 916, 883, 823, 780, 740, 695 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.33–7.32 (m, 4H), 7.26–7.23 (m, 4H), 7.19–7.16 (m, 2H), 6.73 (d, $J=8.9$ Hz, 2H), 6.58 (d, $J=8.9$ Hz, 2H), 6.01 (s, 1H), 4.43 (s, 1H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 152.6, 149.9, 141.7, 128.8, 127.9, 127.2, 117.7, 116.2, 83.0 ppm; HRMS (CI) calcd for $\text{C}_{19}\text{H}_{17}\text{O}_2^+$ $[M+\text{H}]^+$ 277.1229, found 277.1231.

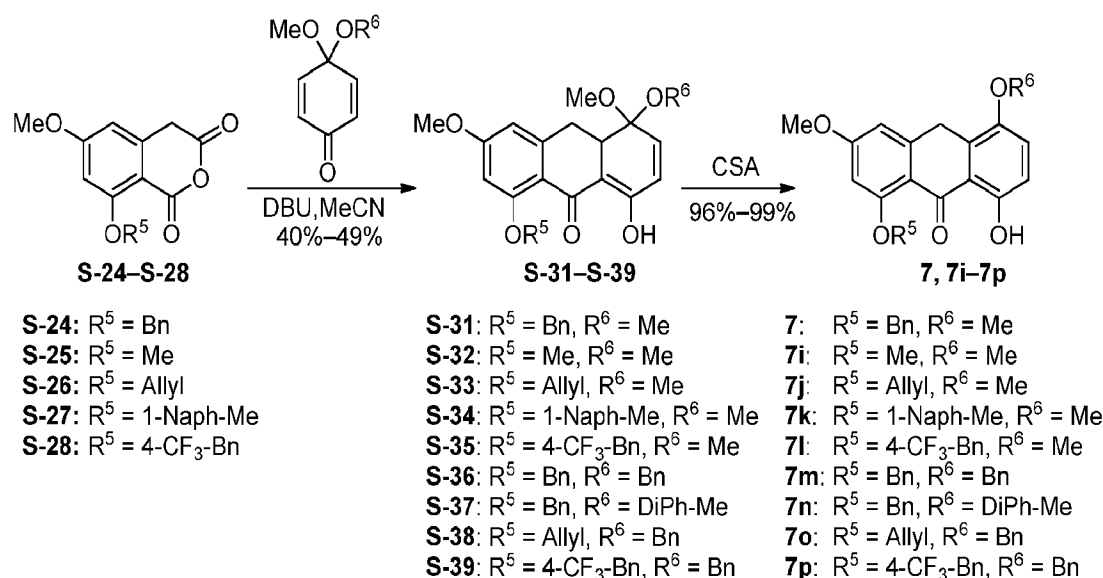
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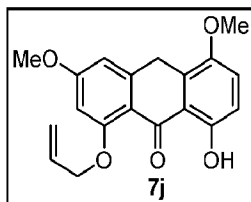


4-(Diphenylmethoxy)-4-methoxycyclohexa-2,5-dien-1-one (S-30): Quinone **S-30** was synthesized according to the reported procedure (Pelter and Elgendy, 1988). To a stirred solution of phenol **S-29** (1.40 g, 5.00 mmol, 1.0 equiv) in MeOH (50 mL) was added iodobenzene diacetate [PhI(OAc)₂, 1.61 g, 5.00 mmol, 1.0 equiv] at 0 °C, and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched by addition of saturated aq. NaHCO₃ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography (silica gel, 2%→5%→10% EtOAc:hexanes, 0.1% Et₃N) to afford semi-quinone **S-30** (1.47 g, 4.80 mmol, 96% yield) as colorless oil. **S-30**: R_f=0.60 (silica gel, EtOAc:hexanes 1:9); FT-IR (neat) ν_{max}: 3029, 2940, 2833, 1687, 1673, 1637, 1494, 1454, 1385, 1318, 1305, 1247, 1176, 1100, 1070, 1019, 973, 918, 856, 775, 743, 702 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.38–7.30 (m, 8 H), 7.29–7.24 (m, 2 H), 6.75 (d, *J*=10.2 Hz, 2 H), 6.15 (d, *J*=10.2 Hz, 2 H), 5.91 (s, 1 H), 3.38 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 185.5, 144.1, 142.7, 129.2, 128.6, 127.7, 126.9, 93.5, 76.5, 51.2 ppm; HRMS (CI) calcd for C₂₀H₁₇O₃⁺ [*M*-H]⁺ 305.1172, found 305.1184.

Scheme 4. Synthesis of Anthrones 7, 7i–7p

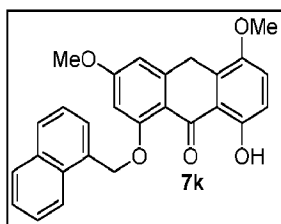


Anthrones **7** and **7i** were prepared following the previously reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). The physical and spectroscopic data of these compounds matched those previously reported (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014).

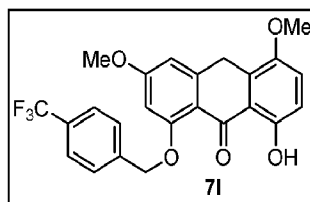


1-(Allyloxy)-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one (7j): Anthrone **7j** was synthesized according to the reported procedure (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014). 4,4-Dimethoxycyclohexa-2,5-dien-1-one³⁵ (463 mg, 3.00 mmol, 3.0 equiv) was dissolved in MeCN (6 mL), and DBU (450 μL, 3.00 mmol,

3.0 equiv) was added. Separately, cyclic anhydride **S-26** (248 mg, 1.00 mmol, 1.0 equiv) was slurried in MeCN (6 mL) and added to the quinone solution at 25 °C over 0.5 h using a syringe pump with constant agitation. After the addition was complete, the mixture was heated to 65 °C for 18 h. The dark mixture was then cooled to 25 °C and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5%→10%→20%→25%→30% EtOAc:hexanes, 0.1% Et₃N) gave the *BCD* tricycle **S-33** (143 mg, 400 μmol, 40% yield) as yellow solid. The obtained *BCD* tricycle **S-33** was dissolved in CH₂Cl₂ (4 mL) at 25 °C and freshly crystallized CSA (1.9 mg, 8.0 μmol, 0.02 equiv) was added. The resulting solution was stirred for 30 min and the reaction was quenched by addition of saturated aq. NaHCO₃ (4 mL). The layers were separated, and the organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give essentially pure anthrone **7j** (130 mg, 400 μmol, quant. yield) as an orange solid. **7j**: R_f=0.20 (silica gel, EtOAc:hexanes 3:7); m.p.=145–146 °C (CH₂Cl₂); FT-IR (film) ν_{max}: 2925, 2840, 1636, 1600, 1476, 1435, 1387, 1351, 1329, 1269, 1230, 1196, 1173, 1115, 1091, 1071, 1058, 1026, 963, 931, 853, 818, 785, 735, 665 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 12.95 (s, 1 H), 6.96 (d, *J*=8.9 Hz, 1 H), 6.79 (d, *J*=8.8 Hz, 1 H), 6.45 (s, 1 H), 6.34 (s, 1 H), 6.11 (ddt, *J*=17.0, 10.1, 4.7 Hz, 1 H), 5.67 (ddd, *J*=17.2, 1.8, 1.8 Hz, 1 H), 5.36 (ddd, *J*=11.0, 1.4, 1.4 Hz, 1 H), 4.63 (d, *J*=3.3 Hz, 2 H), 4.05 (s, 2 H), 3.82 (s, 3 H), 3.81 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 188.8, 164.1, 162.2, 156.3, 147.7, 146.3, 132.5, 127.4, 117.9, 117.5, 116.7, 114.8, 114.5, 104.7, 99.1, 69.6, 56.0, 55.5, 29.0 ppm; HRMS (ESI) calcd for C₁₉H₁₈O₅Na⁺ [*M*+Na]⁺ 349.1046, found 349.1052.

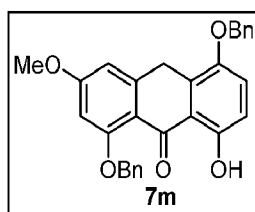


8-Hydroxy-3,5-dimethoxy-1-(1-naphthylmethoxy)anthracen-9(10H)-one (7k): Anthrone **7k** was synthesized according to the procedure described above for the preparation of **7j**. 4,4-Dimethoxy-cyclohexa-2,5-dienone (Frlan *et al.*, 2007) (463 mg, 3.00 mmol, 3.0 equiv) was reacted with **S-27** (426 mg, 1.00 mmol, 1.0 equiv) to give the *BCD* tricycle **S-34** (206 mg, 450 μmol, 45% yield) as yellow solid. The obtained *BCD* tricycle **S-34** was reacted with CSA (2.1 mg, 9.0 μmol, 0.02 equiv) to give essentially pure anthrone **7k** (192 mg, 450 μmol, quant. yield) as an orange solid. **7k**: R_f=0.30 (silica gel, EtOAc:hexanes 3:7); m.p.=172–173 °C (CH₂Cl₂); FT-IR (film) ν_{max}: 2925, 2838, 1636, 1600, 1475, 1432, 1393, 1352, 1329, 1268, 1230, 1195, 1173, 1115, 1101, 1063, 1026, 961, 932, 853, 819, 800, 773, 732 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 13.04 (s, 1 H), 8.09 (d, *J*=8.2 Hz, 1 H), 8.02 (d, *J*=6.8 Hz, 1 H), 7.89 (d, *J*=7.8 Hz, 1 H), 7.83 (d, *J*=8.1 Hz, 1 H), 7.60–7.47 (m, 3 H), 7.02 (d, *J*=8.9 Hz, 1 H), 6.86 (d, *J*=8.8 Hz, 1 H), 6.56 (s, 1 H), 6.52 (s, 1 H), 5.68 (s, 2 H), 4.15 (s, 2 H), 3.85 (s, 3 H), 3.81 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 188.9, 164.2, 162.2, 156.5, 147.9, 146.4, 133.7, 131.9, 130.7, 128.9, 128.5, 127.5, 126.4, 125.9, 125.8, 125.5, 123.2, 117.7, 117.0, 115.3, 114.7, 105.0, 99.9, 69.3, 56.1, 55.6, 29.1 ppm; HRMS (ESI) calcd for C₂₇H₂₂O₅Na⁺ [*M*+Na]⁺ 449.1359, found 449.1361.

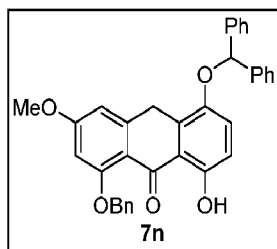


8-Hydroxy-3,5-dimethoxy-1-([4-(trifluoromethyl)benzyl]oxy)anthracen-9(10H)-one (7l):

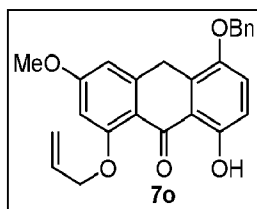
Anthrone **7l** was synthesized according to the procedure described above for the preparation of **7j**. 4,4-Dimethoxy-cyclohexa-2,5-dienone (Frlan *et al.*, 2007) (463 mg, 3.00 mmol, 3.0 equiv) was reacted with **S-28** (366 mg, 1.00 mmol, 1.0 equiv) to give the *BCD* tricycle **S-35** (200 mg, 420 μ mol, 42% yield) as yellow solid. The obtained *BCD* tricycle **S-35** was reacted with CSA (2.0 mg, 8.4 μ mol, 0.02 equiv) to give essentially pure anthrone **7l** (187 mg, 420 μ mol, quant. yield) as an orange solid. **7l**: R_f =0.40 (silica gel, EtOAc:hexanes 3:7); m.p.=165–166 °C (CH_2Cl_2); FT-IR (film) ν_{max} : 2926, 2842, 1637, 1602, 1585, 1476, 1437, 1421, 1382, 1325, 1269, 1230, 1196, 1164, 1120, 1099, 1066, 1027, 1019, 991, 961, 932, 855, 825, 782, 734, 722, 666 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 12.97 (s, 1 H), 7.76 (d, J =8.0 Hz, 2 H), 7.67 (d, J =8.0 Hz, 2 H), 7.02 (d, J =8.9 Hz, 1 H), 6.85 (d, J =8.9 Hz, 1 H), 6.51 (s, 1 H), 6.39 (d, J =1.7 Hz, 1 H), 5.21 (s, 2 H), 4.13 (s, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 188.8, 164.2, 161.7, 156.5, 147.8, 146.5, 140.8, 130.0 (q, J =32.4 Hz), 126.8, 125.7 (q, J =3.3 Hz), 124.3 (q, J =272.0 Hz), 117.6, 117.0, 115.1, 114.7, 113.9, 105.1, 99.5, 69.8, 56.1, 55.6, 29.1 ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -61.54 (s) ppm; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{F}_3\text{O}_5\text{Na}^+ [M+\text{Na}]^+$ 467.1077, found 467.1077.



1,5-Bis(benzyloxy)-8-hydroxy-3-methoxyanthracen-9(10H)-one (7m): Anthrone **7m** was synthesized according to the procedure described above for the preparation of **7j**. 4-(Benzyloxy)-4-methoxycyclohexa-2,5-dienone (Frlan *et al.*, 2007) (691 mg, 3.00 mmol, 3.0 equiv) was reacted with **S-24**³⁰ (298 mg, 1.00 mmol, 1.0 equiv) to give the *BCD* tricycle **S-36** (233 mg, 480 μ mol, 48% yield) as yellow solid. The obtained *BCD* tricycle **S-36** was reacted with CSA (2.3 mg, 9.6 μ mol, 0.02 equiv) to give essentially pure anthrone **7m** (106 mg, 235 μ mol, 49%) and **7** (89.2 mg, 235 μ mol, 49%) as orange solids. **7m**: R_f =0.45 (silica gel, EtOAc:hexanes 3:7); m.p.=89–90 °C (CH_2Cl_2); FT-IR (film) ν_{max} : 2925, 2854, 1633, 1597, 1582, 1498, 1462, 1435, 1384, 1350, 1325, 1266, 1226, 1196, 1165, 1096, 1055, 1025, 991, 963, 905, 868, 814, 735, 696, 656 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 13.08 (s, 1 H), 7.61 (d, J =7.5 Hz, 2 H), 7.53–7.30 (m, 8 H), 7.10 (d, J =8.9 Hz, 1 H), 6.85 (d, J =8.9 Hz, 1 H), 6.53 (s, 1 H), 6.47 (s, 1 H), 5.26 (s, 2 H), 5.09 (s, 2 H), 4.22 (s, 2 H), 3.83 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 189.0, 164.4, 162.4, 156.9, 147.1, 146.4, 137.4, 136.8, 128.9, 128.3, 128.1, 128.0, 127.7, 126.9, 118.8, 117.9, 115.4, 114.9, 105.1, 100.0, 71.2, 70.9, 55.8, 29.3 ppm; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{O}_5\text{Na}^+ [M+\text{Na}]^+$ 475.1516, found 467.1517.

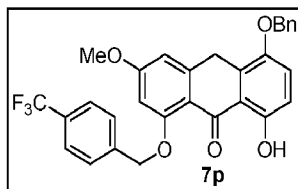


1-(Benzyloxy)-5-(diphenylmethoxy)-8-hydroxy-3-methoxyanthracen-9(10H)-one (7n): Anthrone **7n** was synthesized according to the procedure described above for the preparation of **7j**. 4-(Diphenylmethoxy)-4-methoxycyclohexa-2,5-dien-1-one (**S-30**, 919 mg, 3.00 mmol, 3.0 equiv) was reacted with **S-24**³⁰ (298 mg, 1.00 mmol, 1.0 equiv) to give the *BCD* tricycle **S-37** (233 mg, 400 μ mol, 40%) as yellow solid. The obtained *BCD* tricycle **S-37** was reacted with CSA (1.9 mg, 8.0 μ mol, 0.02 equiv) to give crude anthrone **7n** (100 mg, 192 μ mol, 48% yield) and **7** (71.5 mg, 192 μ mol, 48% yield) as orange solids. **7n**: R_f =0.40 (silica gel, EtOAc:hexanes 3:7); m.p.=72–74 °C (CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2925, 2852, 1664, 1629, 1597, 1509, 1495, 1465, 1454, 1438, 1384, 1361, 1324, 1283, 1259, 1228, 1165, 1082, 1065, 1016, 966, 882, 863, 830, 818, 802, 760, 736, 697 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 13.08 (s, 1 H), 7.55 (d, J =7.6 Hz, 2 H), 7.40 (m, 3 H), 7.36–7.31 (m, 6 H), 7.26 (m, 2 H), 6.92 (d, J =9.0 Hz, 1 H), 6.73 (d, J =1.9 Hz, 2 H), 6.68 (d, J =9.0 Hz, 1 H), 6.48 (s, 1 H), 6.43 (s, 1 H), 6.15 (s, 1 H), 5.21 (s, 2 H), 4.22 (s, 2 H), 3.78 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 188.8, 164.3, 162.2, 156.9, 146.2, 143.9, 141.5, 136.7, 128.8, 128.7, 128.6, 128.1, 128.0, 127.0, 126.8, 120.5, 117.7, 116.2, 114.9, 105.0, 99.8, 82.6, 70.8, 55.7, 29.4 ppm; HRMS (ESI) calcd for C₃₅H₂₈O₅Na⁺ [M +Na]⁺ 551.1829, found 551.1830.



1-(Allyloxy)-5-(benzyloxy)-8-hydroxy-3-methoxyanthracen-9(10H)-one (7o): Anthrone **7o** was synthesized according to the procedure described above for the preparation of **7j**. 4-(Benzyloxy)-4-methoxycyclohexa-2,5-dienone (Frlan *et al.*, 2007) (691 mg, 3.00 mmol, 3.0 equiv) was reacted with **S-26** (248 mg, 1.00 mmol, 1.0 equiv) to give the *BCD* tricycle **S-38** (200 mg, 460 μ mol, 46% yield) as yellow solid. The obtained *BCD* tricycle **S-38** was reacted with CSA (2.2 mg, 9.2 μ mol, 0.02 equiv) to give essentially pure anthrone **7o** (90 mg, 225 μ mol, 49% yield) and **7j** (73 mg, 225 μ mol, 49% yield) as orange solids. **7o**: R_f =0.40 (silica gel, EtOAc:hexanes 3:7); m.p.=118–119 °C (CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2924, 2854, 1634, 1597, 1582, 1474, 1462, 1454, 1384, 1369, 1351, 1326, 1266, 1227, 1195, 1167, 1114, 1089, 1053, 1025, 992, 969, 930, 868, 815, 754, 737, 697, 666 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 13.02 (s, 1 H), 7.49–7.37 (m, 5 H), 7.09 (d, J =8.9 Hz, 1 H), 6.83 (d, J =8.9 Hz, 1 H), 6.53 (s, 1 H), 6.43 (s, 1 H), 6.13 (ddt, J =17.1, 10.4, 4.8 Hz, 1 H), 5.67 (ddd, J =17.2, 1.6, 1.6 Hz, 1 H), 5.37 (ddd, J =10.7, 1.5, 1.5 Hz, 1 H), 5.08 (s, 2 H), 4.70–4.68 (m, 2 H), 4.20 (s, 2 H), 3.86 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 188.8, 164.2, 162.3, 156.7, 146.9, 146.2, 137.2, 132.4,

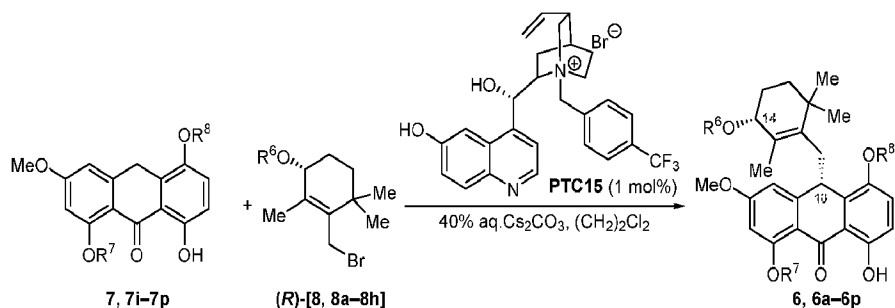
128.7, 128.6, 128.1, 127.5, 118.6, 118.0, 116.1, 114.7, 104.7, 99.4, 71.0, 69.7, 55.6, 29.7, 29.1 ppm; HRMS (ESI) calcd for $C_{25}H_{22}O_5Na^+$ [$M+Na$] $^+$ 425.1359, found 425.1363.



5-(Benzyloxy)-8-hydroxy-3-methoxy-1-[[4-(trifluoromethyl)benzyl]oxy]anthracen-9(10H)-one

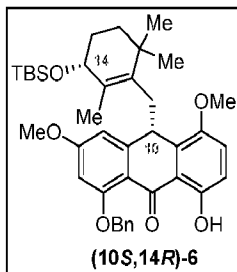
5 **(7p)**: Anthrone **7p** was synthesized according to the procedure described above for the preparation of **7j**. 4-(Benzyloxy)-4-methoxycyclohexa-2,5-dienone (Frlan *et al.*, 2007) (691 mg, 3.00 mmol, 3.0 equiv) was reacted with **S-28** (366 mg, 1.00 mmol, 1.0 equiv) to give the *BCD* tricycle **S-39** (232 mg, 420 μ mol, 42% yield) as yellow solid. The obtained *BCD* tricycle **S-39** was reacted with CSA (2.0 mg, 8.4 μ mol, 0.02 equiv) to give essentially pure anthrone **7p** (108 mg, 206 μ mol, 49% yield) and **7l** (92.0 mg, 206 μ mol, 49% yield) as orange solids. **7p**: R_f = 0.50 (silica gel, EtOAc:hexanes 3:7); m.p. = 95–96 °C (CH_2Cl_2); FT-IR (film) ν_{max} : 2952, 2923, 2854, 1634, 1599, 1586, 1454, 1421, 1380, 1369, 1352, 1323, 1266, 1228, 1196, 1163, 1119, 1098, 1065, 1018, 992, 964, 941, 825, 737, 697, 664 cm^{-1} ; ^1H NMR (600 MHz, $CDCl_3$) δ 13.03 (s, 1 H), 7.72–7.62 (m, 4 H), 7.50–7.35 (m, 5 H), 7.10 (d, J = 8.8 Hz, 1 H), 6.85 (d, J = 8.6 Hz, 1 H), 6.55 (s, 1 H), 6.43 (s, 1 H), 5.26 (s, 2 H), 5.09 (s, 2 H), 4.22 (s, 2 H), 3.85 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.7, 164.2, 161.7, 156.7, 146.9, 146.4, 140.7, 137.1, 129.9 (q, J = 32.2 Hz), 128.7, 128.1, 127.8, 127.5, 126.8, 125.6 (q, J = 3.6 Hz), 124.2 (q, J = 271.8 Hz), 118.7, 117.6, 116.0, 114.8, 104.9, 99.7, 70.9, 69.8, 55.6, 29.1 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ –61.54 (s) ppm; HRMS (ESI) calcd for $C_{30}H_{23}F_3O_5Na^+$ [$M+Na$] $^+$ 543.1390, found 543.1386.

Scheme 5. Asymmetric Alkylation of Anthrones (7, 7i–7p) with Allylic Bromides (R)-[8, 8a–8h] and PTC15

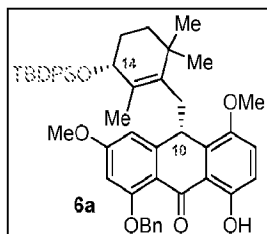


20 **General procedure for the asymmetric alkylation**: To a stirred mixture of anthrone [(**7**, **7i–7p**), 100 μ mol, 1.0 equiv], allylic bromide {(*R*)-[**8**, **8a–8h**]; 110 μ mol, 1.1 equiv} and **PTC15** (1.00 μ mol, 1 mol%, 0.01 equiv) in $(CH_2)_2Cl_2$ (0.9 mL) under argon, was added 40% aq. Cs_2CO_3 solution (0.3 mL) dropwise at –30 °C. The reaction mixture was stirred vigorously and then allowed to warm to –20 °C. Stirring was continued at this temperature for 72 h. The mixture was then quenched by addition of H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2%→5%→10% EtOAc:hexanes) gave the alkylated anthrones (**6**, **6a–6p**) as yellow products.

General procedure for the preparation of racemic alkylated anthrones: To a solution of anthrone [(**7**, **7i**–**7p**), 100 μ mol, 1.0 equiv], allylic bromide {(*R*)-[**8**, **8a**–**8h**]; 110 μ mol, 1.1 equiv} in DMF (1 mL) under argon, was added Na₂CO₃ (10.6 mg, 1.00 mmol, 10 equiv). The reaction mixture was shielded from light and stirred vigorously for 1 h in the dark. The reaction was quenched by addition of water (10 mL) and diluted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (2 $\times$ 10 mL), and the combined organic phases were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude oil, which was purified by flash column chromatography on silica gel (2% $\rightarrow$ 5% $\rightarrow$ 10% EtOAc:hexanes) to give the racemic alkylated anthrones (**6**, **6a**–**6p**) as yellow products.



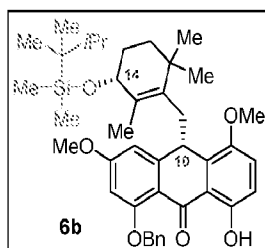
(10*S*)-1-(Benzyloxy)-10-[(3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl)methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10*H*)-one [enantioenriched (**10*S*,14*R*)-6]: yellow foam, 46.3 mg, 72.0 μ mol, 72% yield, 95:5 dr. the diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}$ C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 7.01 min for (**10*R*,14*R*)-6**; 8.05 min for (**10*S*,14*R*)-6**. Enantioenriched (**10*S*,14*R*)-6**: $[\alpha]_D^{22} = +94.7$ ($c = 1.0$, CH₂Cl₂); all other physical and spectroscopic data of this compound matched those mentioned above.**



(10*S*)-1-(Benzyloxy)-10-[(3*R*)-3-[[*tert*-butyl(diphenyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl)methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10*H*)-one [enantioenriched **6a**]: yellow solid, 59.8 mg, 78.0 μ mol, 78% yield, 91:9 dr. the diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}$ C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.99 min for (**10*R*,14*R*)-6a**; 7.30 min for (**10*S*,14*R*)-6a**. Crystallization from hexanes/*i*PrOH 19:1 gave crystals (> 99:1 dr) suitable for X-ray crystallographic analysis, which revealed its absolute configuration for the chiral alkylated anthrones as shown below (**FIG. 2**).

Enantioenriched **6a**: $R_f = 0.40$ (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22} = +69.5$ ($c = 1.0$, CH₂Cl₂, > 99:1 dr); m.p. = 165–166 $^{\circ}$ C (hexanes/*i*PrOH 19:1); FT-IR (film) $\nu_{\max}$: 2934, 2857, 1637, 1599, 1585, 1568, 1474, 1429, 1385, 1352, 1329, 1297, 1267, 1228, 1196, 1166, 1148, 1104, 1077, 1035, 999, 978, 968, 935, 881, 856, 822, 792, 766, 739, 702, 659 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C

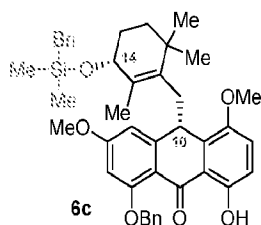
NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.69 (s, 1 H, major), 12.67 (s, 1 H, minor), 7.73 (d, $J=6.3$ Hz, 2 H, minor), 7.69 (d, $J=6.4$ Hz, 2 H, major), 7.58 (d, $J=7.5$ Hz, 2 H, major + minor), 7.49–7.34 (m, 8 H, major + minor), 7.30 (ap t, $J=7.3$ Hz, 1 H, major + minor), 7.06 (d, $J=9.0$ Hz, 1 H, major + minor), 6.87 (d, $J=8.9$ Hz, 1 H, major + minor), 6.47 (b, 1 H, minor), 6.45 (b, 1 H, major), 5.27 (ABq, $\Delta\delta_{\text{AB}}=0.065$, $J=12.5$ Hz, 2 H, major + minor), 4.65 (b, 1 H, major + minor), 4.59 (b, 1 H, minor), 4.02–3.58 (m, 4 H, major + minor), 3.88 (s, 3 H, major + minor), 2.65 (d, $J=12.4$ Hz, 1 H, major + minor), 2.10–0.02 (m, 15 H, major + minor), 1.08 (s, 9 H, major), 1.05 (s, 9 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* δ 188.59 (major), 188.55 (minor), 163.74 (major), 163.64 (minor), 162.0 (major + minor), 156.30 (major), 156.25 (minor), 150.09 (b, major + minor), 147.72 (major + minor), 136.70 (major + minor), 136.24 (major + minor), 136.18 (major + minor), 135.3 (minor), 135.0 (major), 134.9 (major + minor), 134.1 (major + minor), 133.4 (major + minor), 129.77 (minor), 129.72 (major), 129.65 (minor), 129.57 (major), 128.72 (major + minor), 127.8 (major + minor), 127.7 (major), 127.6 (minor), 127.5 (major + minor), 117.80 (major + minor), 117.74 (major + minor), 115.13 (major + minor), 115.10 (major + minor), 107.1 (b, major + minor), 99.8 (major + minor), 73.6 (b, major + minor), 70.8 (major + minor), 56.08 (minor), 56.03 (major), 55.65 (major), 55.48 (minor), 41.14 (b, major + minor), 39.1 (b, major + minor), 35.94 (major + minor), 29.27 (major + minor), 28.65 (major + minor), 27.42 (major + minor), 26.70 (major + minor), 19.62 (major + minor) ppm; HRMS (ESI) calcd for $\text{C}_{49}\text{H}_{54}\text{O}_6\text{SiNa}^+ [M+\text{Na}]^+$ 789.3582 found 789.3575. *Due to signal broadening, not all the ^{13}C signals could be identified.



(10S)-1-(Benzyloxy)-10-[(3R)-3-[(2,3-dimethylbutan-2-yl)(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [enantioenriched **6b**]: yellow foam, 49.7 mg, 74.0 μmol , 74% yield, 95:5 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^\circ\text{C}$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.52 min for **(10R,14R)-6b**, 6.19 min for **(10S,14R)-6b**.

Enantioenriched **6b**: $R_f=0.55$ (silica gel, EtOAc:hexanes 1:4); $[\alpha]_{\text{D}}^{22} = +81.6$ ($c=1.0$, CH_2Cl_2); FT-IR (film) ν_{max} : 2956, 2865, 1639, 1600, 1585, 1569, 1475, 1433, 1384, 1353, 1329, 1297, 1267, 1229, 1196, 1171, 1148, 1102, 1077, 1033, 1003, 980, 968, 935, 882, 856, 829, 775 737, 696 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.68 (s, 1 H, major), 12.67 (s, 1 H, minor), 7.57 (d, $J=7.4$ Hz, 2 H, major + minor), 7.39 (ap t, $J=7.6$ Hz, 2 H, major + minor), 7.30 (ap t, $J=7.4$ Hz, 1 H, major + minor), 7.05 (d, $J=9.0$ Hz, 1 H, major + minor), 6.86 (d, $J=8.9$ Hz, 1 H, major + minor), 6.44 (d, $J=2.2$ Hz, 2 H, major), 6.43 (d, $J=2.2$ Hz, 2 H, minor), 6.38 (b, 1 H, major), 6.29 (b, 1 H, minor), 5.26 (ABq, $\Delta\delta_{\text{AB}}=0.072$, $J=12.6$ Hz, 2 H, major + minor), 4.62 (b, 1 H, major + minor), 3.95 (b, 1 H, major + minor), 3.89 (s, 3 H, major + minor), 3.82 (s, 3 H, major +

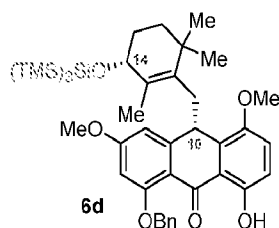
minor), 2.68 (d, $J=11.3$ Hz, 1 H, major + minor), 1.99–0.82 (m, 14 H, major + minor), 0.94–0.83 (m, 13 H, major + minor), 0.14 (s, 3 H, major), 0.12 (s, 3 H, major), 0.09 (s, 3 H, minor) 0.07 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* 188.63 (major), 188.58 (minor), 163.75 (major), 163.67 (minor), 162.1 (major + minor), 156.30 (major + minor), 150.2 (b, major + minor), 147.74 (major + minor), 136.71 (major + minor), 133.52 (major + minor), 128.73 (major + minor), 127.83 (major + minor), 126.8 (major + minor), 117.82 (major + minor), 117.75 (major + minor), 115.11 (major + minor), 115.08 (major + minor), 107.17 (major + minor), 99.84 (major + minor), 72.5 (b, major + minor), 70.8 (major + minor), 56.14 (minor), 56.07 (major), 55.70 (major), 55.59 (minor), 41.30 (b, major + minor), 38.85 (b, major + minor), 36.33 (b, major + minor), 35.96 (major + minor), 34.02 (major + minor), 29.76 (major + minor), 29.17 (b, major + minor), 25.51 (major + minor), 25.11 (major + minor), 20.38 (major + minor), 20.32 (major + minor), 18.77 (major + minor), 18.73 (major + minor), –1.73 (major), –1.87 (minor), –2.52 (major + minor) ppm; HRMS (ESI) calcd for $\text{C}_{41}\text{H}_{54}\text{O}_6\text{SiNa}^+ [M+\text{Na}]^+$ 693.3582, found 693.3583. *Due to signal broadening, not all the ^{13}C signals could be identified.



(10S)-10-[(3R)-3-[(Benzyl(dimethyl)silyl)oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-1-(benzyloxy)-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [enantioenriched **6c**]: yellow foam, 46.0 mg, 68.0 μmol , 68% yield, 88:12 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^\circ\text{C}$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 4.31 min for (**10R,14R**)-**6c**, 5.26 min for (**10S,14R**)-**6c**.

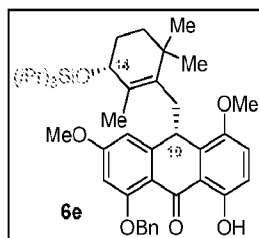
Enantioenriched **6c**: $R_f=0.48$ (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22} = +78.6$ ($c=1.0$, CH_2Cl_2); FT-IR (film) ν_{max} : 2936, 2863, 1637, 1600, 1584, 1568, 1492, 1475, 1453, 1432, 1384, 1353, 1330, 1297, 1268, 1230, 1207, 1167, 1102, 1058, 1033, 1002, 980, 968, 935, 882, 835, 763, 738, 698 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.73 (s, 1 H, minor), 12.68 (s, 1 H, major), 7.57 (d, $J=7.5$ Hz, 2 H, major + minor), 7.39 (dd, $J=15.3, 7.7$ Hz, 2 H, major + minor), 7.30 (ap t, $J=7.5$ Hz, 1 H, major + minor), 7.24–7.20 (m, 2 H, major + minor), 7.09–7.03 (m, 3 H, major + minor), 6.86 (d, $J=8.9$ Hz, 1 H, major + minor), 6.47 (s, 1 H, minor), 6.45 (s, 1 H, major), 6.38 (b, 1 H, major), 6.27 (b, 1 H, minor), 5.25 (ABq, $\Delta\delta_{\text{AB}}=0.073$, $J=12.5$ Hz, 2 H, major + minor), 4.64 (b, 1 H, major), 4.55 (b, 1 H, minor), 3.96 (b, 1 H, major + minor), 3.91 (s, 3 H, minor), 3.89 (s, 3 H, major), 3.82 (s, 3 H, minor), 3.80 (s, 3 H, major), 2.69 (b, 1 H, major + minor), 2.16–0.56 (m, 17 H, major + minor), 0.14 (s, 3 H, minor), 0.09 (s, 3 H, major), 0.05 (s, 3 H, major), 0.02 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* 188.59 (major), 188.56 (minor), 163.78 (major), 163.73 (minor), 161.94 (major + minor), 156.35 (minor), 156.30 (major), 147.76 (major), 147.67 (minor), 139.43 (minor), 139.25 (major), 136.72 (minor), 136.70 (major), 133.35 (major + minor), 128.72 (major + minor), 128.56 (minor), 128.53 (major), 128.38 (major), 128.30 (minor), 127.81 (major + minor), 126.79 (major + minor), 117.78 (major + minor),

117.75 (major), 117.71 (minor), 115.19 (major + minor), 115.14 (major), 115.01 (minor), 106.51 (major + minor), 100.33 (major + minor), 72.5 (b, major + minor), 70.8 (major + minor), 64.6 (major + minor), 56.10 (minor), 56.03 (major), 55.72 (major), 55.50 (minor), 40.8 (b, major + minor), 35.91 (minor), 35.84 (major), 31.06 (major + minor), 29.55 (major), 29.36 (minor), 28.9 (minor), 28.64 (major), 27.58 (major + minor), 25.51 (major + minor), -1.54 (major + minor), -1.57 (major), -1.68 (minor) ppm; HRMS (ESI) calcd for $C_{42}H_{48}O_6SiNa^+ [M+Na]^+$ 699.3112, found 699.3109. *Due to signal broadening, not all the ^{13}C signals could be identified.



(10S)-1-(Benzyloxy)-10-[[[(3R)-3-[[1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilan-2-yl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one
 [enantioenriched **6d**]: yellow foam, 42.6 mg, 55.0 μ mol, 55% yield, 95:5 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}C$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 4.02 min for **(10R,14R)-6d**, 4.82 min for **(10S,14R)-6d**.

Enantioenriched **6d**: R_f =0.45 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22} = +82.9$ (c =1.0, CH_2Cl_2); FT-IR (film) ν_{max} : 2946, 2895, 1638, 1600, 1585, 1570, 1475, 1453, 1433, 1385, 1328, 1298, 1267, 1243, 1228, 1170, 1102, 1062, 1033, 999, 972, 834, 739, 694 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond, ^1H NMR (600 MHz, $CDCl_3$) δ 12.69 (s, 1 H, minor), 12.67 (s, 1 H, major), 7.57 (d, J =7.4 Hz, 2 H, major + minor), 7.39 (ap t, J =7.6 Hz, 2 H, major + minor), 7.30 (ap t, J =7.4 Hz, 1 H, major + minor), 7.05 (d, J =9.0 Hz, 1 H, major + minor), 6.86 (d, J =8.9 Hz, 1 H, major + minor), 6.45 (d, J =2.0 Hz, 1 H, minor), 6.44 (d, J =2.0 Hz, 1 H, major), 6.36 (b, 1 H, major), 6.29 (b, 1 H, minor), 5.25 (ABq, $\Delta\delta_{AB}$ =0.073, J =12.6 Hz, 1 H, major + minor), 4.62 (b, 1 H, major + minor), 3.90 (s, 3 H, minor), 3.89 (s, 3 H, major), 3.83 (s, 3 H, minor), 3.81 (s, 3 H, major), 3.67 (b, 1 H, major + minor), 2.64 (d, J =11.4 Hz, 1 H, major + minor), 1.95–0.75 (m, 14 H, major + minor), 0.21 (s, 27 H, major), 0.19 (s, 27 H, minor) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 187.60 (major), 187.57 (minor), 162.8 (major + minor), 161.1 (major + minor), 155.3 (major + minor), 149.1 (b, major + minor), 146.8 (major + minor), 135.73 (minor), 135.71 (minor), 132.3 (major + minor), 127.7 (major + minor), 126.8 (major + minor), 125.8 (major + minor), 116.8 (major + minor), 116.74 (major), 116.69 (minor), 114.2 (major + minor), 114.1 (major + minor), 105.9 (b, major + minor), 98.8 (b, major + minor), 69.9 (major + minor), 55.1 (major + minor), 54.7 (major), 54.5 (minor), 40.1 (b, major + minor), 35.0 (major + minor), 28.9 (major + minor), 28.2 (major + minor), 27.7 (major + minor), -0.1 (major + minor) ppm; HRMS (ESI) calcd for $C_{42}H_{62}O_6Si_4Na^+ [M+Na]^+$ 797.3516, found 797.3518. *Due to signal broadening, not all the ^{13}C signals could be identified.



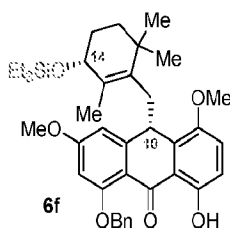
(10S)-1-(Benzyloxy)-8-hydroxy-3,5-dimethoxy-10-((3R)-2,6,6-trimethyl-3-

[(triisopropylsilyl)oxy]cyclohex-1-en-1-yl)methyl)anthracen-9(10H)-one [enantioenriched **6e**]: yellow foam,

51.4 mg, 75.0 μ mol, 75% yield, 92:8 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H,

25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.74 min for (**10R,14R**)-**6e**, 6.45 min (**10S,14R**)-**6e**.

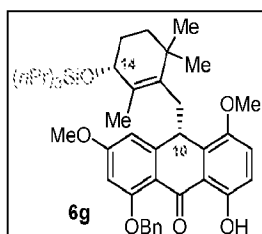
Enantioenriched **6e**: R_f =0.52 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +90.6 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2941, 2865, 1637, 1600, 1584, 1569, 1472, 1433, 1384, 1350, 1329, 1297, 1267, 1229, 1170, 1102, 1054, 1054, 1042, 1033, 1003, 967, 934, 883, 824, 737, 677 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR) due to hindered bond rotation of the newly-formed C–C bond; ¹H NMR (600 MHz, CDCl₃) δ 12.68 (s, 1 H, major), 12.65 (s, 1 H, minor), 7.56 (d, J =7.5 Hz, 2 H, major + minor), 7.39 (ap t, J =7.4 Hz, 2 H, major + minor), 7.30 (ap t, J =7.4 Hz, 1 H, major + minor), 7.06 (d, J =8.9 Hz, 1 H, major + minor), 6.86 (d, J =8.9 Hz, 1 H, major + minor), 6.44 (s, 1 H, major), 6.42 (s, 1 H, minor), 6.40 (b, 1 H, major), 6.31 (b, 1 H, minor), 5.26 (ABq, $\Delta\delta_{AB}$ =0.067, J =10.6 Hz, 2 H, major + minor), 4.65 (b, 1 H, major), 4.60 (b, 1 H, minor), 4.14 (b, 1 H, major), 4.04 (b, 1 H, minor), 3.90 (s, 3 H, major + minor), 3.82 (s, 3 H, major + minor), 2.69 (b, 1 H, major + minor), 2.16–0.55 (m, 14 H, major + minor), 1.10 (s, 18 H, major + minor), 1.05 (s, 3 H, major + minor) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 188.62 (major), 188.58 (minor), 163.74 (major), 163.67 (minor), 162.01 (major), 161.88 (minor), 156.31 (major), 156.28 (minor), 150.2 (b, major + minor), 147.73 (major), 147.66 (minor), 136.7 (major + minor), 133.5 (major + minor), 128.7 (major + minor), 127.8 (major + minor), 126.78 (major), 126.75 (minor), 117.8 (major + minor), 117.73 (major), 117.70 (minor), 115.1 (major + minor), 107.0 (major), 106.4 (minor), 100.0 (b, major + minor), 72.8 (b, major + minor), 70.8 (major + minor), 56.1 (major + minor), 55.7 (major), 55.6 (minor), 40.9 (b, major + minor), 39.0 (b, major + minor), 35.9 (major + minor), 29.9 (major + minor), 29.1 (minor), 29.0 (major), 18.54 (major), 18.50 (minor), 18.47 (major), 18.44 (minor), 17.84 (major + minor), 13.0 (major), 12.98 (minor), 12.4 (major + minor) ppm; HRMS (ESI) calcd for C₄₂H₅₆O₆SiNa⁺ [M +Na]⁺ 707.3738, found 707.3742. *Due to signal broadening, not all the ¹³C signals could be identified.



(10S)-1-(Benzyloxy)-8-hydroxy-3,5-dimethoxy-10-((3R)-2,6,6-trimethyl-3-

[(triethylsilyl)oxy]cyclohex-1-en-1-yl)methyl)anthracen-9(10H)-one [enantioenriched **6f**]: yellow foam, 49.5 mg, 77.0 μ mol, 77% yield, 93:7 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 4.74 min for **(10R,14R)-6f**, 5.50 min for **(10S,14R)-6f**.

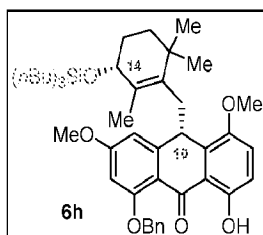
Enantioenriched **6f**: R_f =0.56 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = + 87.1 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2954, 2936, 2875, 1637, 1600, 1584, 1568, 1475, 1432, 1384, 1353, 1329, 1296, 1267, 1230, 1171, 1102, 1075, 1060, 1033, 1002, 967, 934, 880, 825, 738, 696 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR) due to hindered bond rotation of the newly-formed C–C bond; ¹H NMR (600 MHz, CDCl₃) δ 12.72 (s, 1 H, minor), 12.68 (s, 1 H, major), 7.56 (d, J =7.5 Hz, 2 H, major + minor), 7.39 (ap t, J =7.5 Hz, 2 H, major + minor), 7.30 (ap t, J =7.2 Hz, 1 H, major + minor), 7.05 (d, J =8.9 Hz, 1 H, major + minor), 6.86 (d, J =8.9 Hz, 1 H, major + minor), 6.47 (s, 1 H, minor), 6.44 (s, 1 H, major), 6.40 (b, 1 H, major), 6.29 (b, 1 H, minor), 5.25 (ABq, $\Delta\delta_{AB}$ =0.068, J =12.6 Hz, 2 H, major + minor), 4.65 (b, 1 H, major), 4.57 (b, 1 H, minor), 3.96 (b, 1 H, 4.65 (b, 1 H, major + minor), 3.89 (s, 3 H, major + minor), 3.86 (s, 3 H, major), 3.82 (s, 3 H, minor), 2.70 (b, 1 H, major + minor), 2.05–0.79 (m, 14 H, major + minor), 0.98 (t, J =5.9 Hz, 9 H, major + minor) 0.61 (q, J =7.8 Hz, 6 H, major + minor) ppm; ¹³C NMR (151 MHz, CDCl₃)* δ 188.62 (major), 188.57 (minor), 163.7 (major + minor), 161.9 (major + minor), 156.3 (major + minor), 147.75 (major), 147.69 (minor), 136.7 (major + minor), 133.5 (major + minor), 128.7 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.8 (major + minor), 117.6 (major + minor), 115.2 (major + minor), 115.1 (major + minor), 106.4 (b, major + minor), 100.5 (b, major + minor), 72.3 (b, major + minor), 70.8 (major + minor), 56.10 (minor), 56.05 (major), 55.8 (major), 55.62 (minor), 55.40.9 (b, major + minor), 35.91 (minor), 35.86 (major), 29.78 (major), 29.65 (minor), 28.9 (minor), 28.8 (major), 7.13 (major), 7.09 (minor), 5.22 (major), 5.13 (minor) ppm; HRMS (ESI) calcd for C₃₉H₅₀O₆SiNa⁺ [M +Na]⁺ 665.3269, found 665.3268. *Due to signal broadening, not all the ¹³C signals could be identified.

**(10S)-1-(Benzyloxy)-8-hydroxy-3,5-dimethoxy-10-((3R)-2,6,6-trimethyl-3-**

[(tripropylsilyl)oxy]cyclohex-1-en-1-yl)methyl)anthracen-9(10H)-one [enantioenriched **6g**]: yellow foam, 50.0 mg, 73.0 μ mol, 73% yield, 89:11 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 4.31 min for **(10R,14R)-6g**, 5.26 min for **(10S,14R)-6g**.

Enantioenriched **6g**: R_f =0.54 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = + 82.2 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2953, 2926, 2867, 1637, 1600, 1584, 1569, 1475, 1432, 1384, 1353, 1329, 1297, 1229, 1205, 1171,

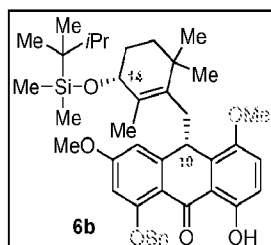
1102, 1033, 1003, 967, 934, 856, 798, 749, 695 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.73 (s, 1 H, minor), 12.68 (s, 1 H, major), 7.57 (d, $J=7.3$ Hz, 2 H, major + minor), 7.39 (ap t, $J=7.6$ Hz, 2 H, major + minor), 7.30 (ap t, $J=7.4$ Hz, 1 H, major + minor), 7.05 (d, $J=8.9$ Hz, 1 H, major + minor), 6.86 (d, $J=9.0$ Hz, 1 H, major + minor), 6.46–6.43 (m, 1 H, major + minor), 6.39 (b, 1 H, major), 6.29 (b, 1 H, minor), 5.30–5.20 (m, 2 H, major + minor), 4.65 (b, 1 H, major), 4.56 (b, 1 H, minor), 3.96 (b, 1 H, major + minor), 3.90 (s, 3 H, major + minor), 3.85 (s, 3 H, major + minor), 2.69 (b, 1 H, major + minor), 2.12–0.68 (m, 14 H, major + minor), 1.44–1.34 (m, 6 H, major + minor), 1.03–0.94 (m, 9 H, major + minor), 0.64–0.53 (m, 6 H, major + minor) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 188.62 (major), 188.56 (minor), 163.8 (major + minor), 161.9 (major), 161.8 (minor), 156.3 (major + minor), 150.3 (b, major + minor), 147.8 (major), 147.7 (minor), 136.7 (major + minor), 133.5 (major + minor), 128.7 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.76 (major + minor), 117.74 (major + minor), 115.2 (major + minor), 115.1 (major + minor), 106.3 (b, major + minor), 100.3 (b, major + minor), 72.4 (b, major + minor), 70.8 (major + minor), 56.10 (minor), 56.05 (major), 55.7 (b, major), 55.6 (minor), 40.9 (b, major + minor), 35.91 (minor), 35.86 (major), 29.8 (major), 29.7 (minor), 28.89 (minor), 28.86 (major), 18.8 (major + minor), 17.36 (major), 17.27 (minor), 17.09 (major), 17.02 (minor) ppm; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{56}\text{O}_6\text{SiNa}^+ [M+\text{Na}]^+$ 707.3738, found 707.3737. *Due to signal broadening, not all the ^{13}C signals could be identified.



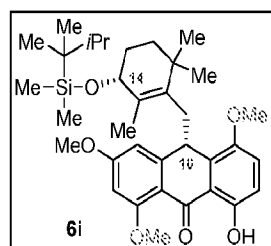
**(10S)-1-(Benzyloxy)-8-hydroxy-3,5-dimethoxy-10-((3R)-2,6,6-trimethyl-3-
 20 [(tributylsilyloxy)cyclohex-1-en-1-yl)methyl]anthracen-9(10H)-one** [enantioenriched **6h**]: yellow foam, 50.9 mg, 70.0 μmol , 70% yield, 89:11 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^\circ\text{C}$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 4.00 min for **(10R,14R)-6h**, 4.69 min for **(10S,14R)-6h**.

Enantioenriched **6h**: $R_f=0.50$ (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}=+77.0$ ($c=1.0$, CH_2Cl_2); FT-IR (film) ν_{max} : 2955, 2923, 2870, 2857, 1637, 1600, 1569, 1475, 1383, 1352, 1329, 1297, 1229, 1205, 1197, 1171, 1102, 1178, 1054, 1002, 966, 934, 887, 856, 790, 765, 695 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.73 (s, 1 H, minor), 12.68 (s, 1 H, major), 7.57 (d, $J=7.3$ Hz, 2 H, major + minor), 7.39 (ap t, $J=7.6$ Hz, 2 H, major + minor), 7.30 (ap t, $J=7.4$ Hz, 1 H, major + minor), 7.05 (d, $J=8.9$ Hz, 1 H, major + minor), 6.86 (d, $J=9.0$ Hz, 1 H, major + minor), 6.45 (d, $J=2.0$ Hz, 1 H, major + minor), 6.39 (b, 1 H, major), 5.29 (b, 1 H, minor), 5.25 (ABq, $\Delta\delta_{\text{AB}}=0.070$, $J=12.8$ Hz, 1 H, major + minor), 4.65 (b, 1 H, major), 4.56 (b, 1 H, minor), 3.96 (b, 1 H, major + minor), 3.90 (s, 3 H, major + minor), 3.85 (s, 3 H, major + minor), 2.69 (b, 1 H, major + minor), 2.22–0.68 (m, 14 H, major + minor), 1.39–1.26 (m, 12 H, major + minor), 0.91 (t, $J=7.2$ Hz,

9 H, major + minor), 0.65–0.55 (m, 6 H, major + minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* δ 188.62 (major), 188.57 (minor), 163.8 (major + minor), 161.92 (major), 161.86 (minor), 156.3 (major + minor), 150.3 (b, major + minor), 147.8 (major), 147.7 (minor), 136.7 (major + minor), 133.5 (major + minor), 128.7 (major + minor), 127.8 (major + minor), 126.8 (major + minor), 117.76 (major + minor), 117.74 (major), 117.72 (minor), 115.2 (major + minor), 115.1 (major + minor), 106.3 (b, major + minor), 100.5 (b, major + minor), 72.3 (b, major + minor), 70.8 (major + minor), 56.09 (minor), 56.06 (major), 55.76 (b, major), 55.59 (minor), 40.9 (b, major + minor), 35.93 (minor), 35.88 (major), 29.8 (major), 29.7 (minor), 28.91 (minor), 28.87 (major), 26.9 (major), 26.7 (minor), 25.7 (major), 25.6 (minor), 14.9 (minor), 14.2 (major), 14.1 (minor), 13.9 (major) ppm; HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{62}\text{O}_6\text{SiNa}^+ [M+\text{Na}]^+$ 749.4208, found 749.4216. *Due to signal broadening, not all the ^{13}C signals could be identified.



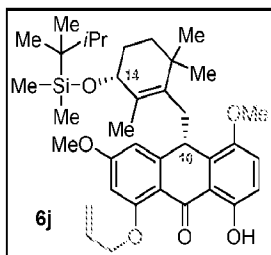
(10S)-1-(Benzyloxy)-10-[[[(3R)-3-[(2,3-dimethylbutan-2-yl)(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [enantioenriched **6b**]: yellow foam, 49.7 mg, 74.0 μmol , 74% yield, 95:5 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^\circ\text{C}$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.59 min for **(10R,14R)-6b**, 6.49 min for **(10S,14R)-6b**. Enantioenriched **6b**: R_f =0.55 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +82.0 (c =1.0, CH_2Cl_2); all other physical and spectroscopic data of this compound matched those mentioned above.



(10S)-10-[[[(3R)-3-[(2,3-Dimethylbutan-2-yl)(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-1,3,5-trimethoxyanthracen-9(10H)-one [enantioenriched **6i**]: yellow foam, 42.8 mg, 72.0 μmol , 72% yield, 90.4:9.6 dr. The diastereomeric ratio was determined by HPLC after benzylation of the alkylated anthrone **6i** (Chiralcel AD-H, 25 $^\circ\text{C}$, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 5.51 min for benzylated **(10R,14R)-6i**, 7.04 min for benzylated **(10S,14R)-6i**.

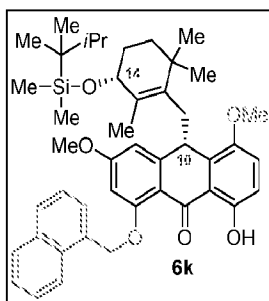
Enantioenriched **6i**: R_f =0.30 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +52.3 (c =1.0, CH_2Cl_2); FT-IR (film) ν_{max} : 2957, 2930, 2869, 1726, 1638, 1600, 1571, 1468, 1378, 1355, 1330, 1286, 1268, 1229, 1200, 1163, 1147, 1121, 1104, 1075, 1034, 1003, 965, 935, 883, 831, 767, 741 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR

(600 MHz, CDCl₃) δ 12.53 (s, 1 H, major), 12.51 (s, 1 H, minor), 7.04 (d, $J=9.0$ Hz, 1 H, major + minor), 6.84 (d, $J=8.9$ Hz, 1 H, major + minor), 6.42 (d, $J=2.1$ Hz, 1 H, major), 6.40 (d, $J=2.3$ Hz, 1 H, minor), 6.38 (b, 1 H, major), 6.30 (b, 1 H, minor), 4.62 (b, 1 H, major + minor), 3.99–3.93 (m, 1 H, major + minor), 3.95 (s, 3 H, major), 3.94 (s, 3 H, minor), 3.892 (s, 3 H, minor), 3.886 (s, 3 H, major), 3.874 (s, 3 H, major), 3.868 (s, 3 H, minor), 2.68 (d, $J=13.1$ Hz, 1 H, major + minor), 2.02–0.80 (m, 14 H, major + minor), 0.94–0.83 (m, 13 H, major + minor), 0.14 (s, 3 H, major), 0.13 (s, 3 H, major), 0.10 (s, 3 H, minor), 0.08 (s, 3 H, minor) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 188.78 (major), 188.74 (minor), 164.01 (major), 163.92 (minor), 163.31 (major), 163.19 (minor), 156.26 (major), 156.24 (minor), 150.4 (b, major + minor), 147.72 (major), 147.64 (minor), 133.7 (minor), 133.5 (major), 117.9 (major), 117.8 (minor), 117.69 (minor), 117.67 (major), 115.1 (major + minor), 114.5 (major + minor), 106.6 (major), 106.1 (minor), 98.2 (minor), 98.0 (major), 72.6 (b, major + minor), 56.3 (major + minor), 56.13 (minor), 56.05 (major), 55.8 (major), 55.6 (minor), 41.3 (b, major), 40.8 (b, minor), 39.1 (b, major + minor), 36.3 (major + minor), 36.0 (major + minor), 34.0 (major), 33.9 (minor), 29.8 (major), 29.7 (minor), 29.2 (major), 29.1 (minor), 25.11 (major), 25.07 (minor), 20.4 (major + minor), 20.3 (major + minor), 18.8 (major + minor), 18.7 (major + minor), –1.7 (major), –1.8 (minor), –2.5 (major + minor) ppm; HRMS (ESI) calcd for C₃₅H₅₀O₆SiNa⁺ [$M+Na$]⁺ 617.3269, found 617.3265. *Due to signal broadening, not all the ¹³C signals could be identified.



(10S)-1-(Allyloxy)-10-[[[(3R)-3-[[[(2,3-dimethylbutan-2-yl)(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [enantioenriched **6j**]: yellow foam, 46.6 mg, 75.0 μ mol, 75% yield, 93:7 dr. The diastereomeric ratio was determined by HPLC after benzylation of the alkylated anthrone **6j** (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 6.03 min for benzylation of **(10R,14R)-6j**, 7.89 min for benzylation of **(10S,14R)-6j**. Enantioenriched **6j**: $R_f=0.36$ (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22} = +89.8$ ($c=1.0$, CH₂Cl₂); FT-IR (film) ν_{max} : 2955, 2935, 2865, 1638, 1600, 1568, 1475, 1435, 1353, 1328, 1297, 1267, 1228, 1197, 1173, 1149, 1117, 1099, 1077, 1052, 1042, 1033, 1002, 966, 934, 883, 830, 766, 670 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR) due to hindered bond rotation of the newly-formed C–C bond; ¹H NMR (600 MHz, CDCl₃) δ 12.61 (s, 1 H, major), 12.59 (s, 1 H, minor), 7.04 (d, $J=9.0$ Hz, 1 H, major + minor), 6.84 (d, $J=8.9$ Hz, 1 H, major + minor), 6.41 (d, $J=2.0$ Hz, 1 H, major), 6.39 (d, $J=2.2$ Hz, 1 H, minor), 6.38 (b, 1 H, major), 6.29 (b, 1 H, minor), 6.16–6.05 (m, 1 H, major + minor), 5.63 (ap dq, $J=17.3, 1.7$ Hz, 1 H, major + minor), 5.35 (ap dq, $J=10.7, 1.6$ Hz, 1 H, major + minor), 4.75–4.68 (m, 1 H, major + minor), 4.67–4.49 (m, 2 H, major + minor), 3.96 (b, 1 H, major + minor), 3.893 (s, 3 H, minor), 3.887 (s, 3 H, major), 3.857 (s, 3 H, major + minor), 2.68 (d, $J=13.1$ Hz, 1 H, major + minor), 2.02–0.80 (m, 14 H, major + minor), 0.94–0.83 (m, 13 H, major + minor), 0.14 (s, 3 H, major), 0.13 (s, 3 H, major), 0.10 (s, 3 H, minor), 0.08 (s, 3 H, minor) ppm; ¹³C NMR (151 MHz, CDCl₃)*

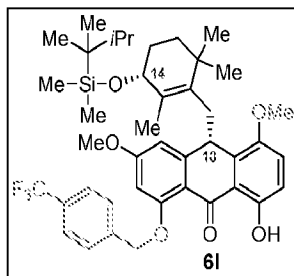
δ 188.63 (major), 188.58 (minor), 163.77 (major), 163.68 (minor), 162.13 (major), 162.00 (minor), 156.27 (major), 156.24 (minor), 150.2 (b, major + minor), 147.71 (major), 147.63 (minor), 133.5 (major + minor), 132.53 (major + minor), 117.91 (major + minor), 117.8 (major + minor), 117.74 (major), 117.68 (minor), 115.1 (major + minor), 114.9 (major + minor), 106.9 (major), 106.4 (minor), 99.4 (b, major + minor), 72.6 (b, major + minor), 69.8 (major + minor), 56.12 (minor), 56.05 (major), 55.72 (major), 55.59 (minor), 41.3 (b, major + minor), 38.9 (b, major + minor), 36.3 (b, major + minor), 36.0 (major + minor), 34.0 (major), 33.9 (minor), 29.8 (major), 29.7 (minor), 29.13 (major), 29.07 (minor), 25.11 (major), 25.07 (minor), 20.4 (major + minor), 20.3 (major + minor), 18.77 (major + minor), 18.73 (major + minor), -1.72 (major), -1.82 (minor), -2.52 (major + minor) ppm; HRMS (ESI) calcd for $C_{37}H_{52}O_6SiNa^+$ $[M+Na]^+$ 643.3425, found 643.3424. *Due to signal broadening, not all the ^{13}C signals could be identified.



(10S)-10-[[3R)-3-[(2,3-Dimethylbutan-2-yl)(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxy-1-(1-naphthylmethoxy)anthracen-9(10H)-one [enantioenriched **6k**]: yellow foam, 50.5 mg, 70.0 μ mol, 70% yield, 92:8 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}C$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 4.29 min for **(10R,14R)-6k**, 5.18 min for **(10S,14R)-6k**.

Enantioenriched **6k**: R_f =0.43 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +66.6 (c =1.0, CH_2Cl_2); FT-IR (film) ν_{max} : 2955, 2928, 2863, 1637, 1600, 1568, 1474, 1433, 1355, 1328, 1298, 1267, 1229, 1197, 1174, 1149, 1105, 1078, 1052, 1043, 1033, 1002, 967, 934, 883, 853, 830, 794, 771, 739 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C-C bond; ^1H NMR (600 MHz, $CDCl_3$) δ 12.66 (s, 1 H, major), 12.64 (s, 1 H, minor), 8.12–8.06 (m, 1 H, major + minor), 7.95 (d, J =6.9 Hz, 1 H, major + minor), 7.89 (d, J =7.5 Hz, 1 H, major + minor), 7.82 (d, J =8.2 Hz, 1 H, major + minor), 7.57–7.48 (m, 3 H, major + minor), 7.06 (d, J =9.0 Hz, 1 H, major + minor), 6.86 (d, J =9.0 Hz, 1 H, major + minor), 6.55 (d, J =2.3 Hz, 1 H, major), 6.53 (d, J =2.3 Hz, 1 H, minor), 6.40 (b, 1 H, major), 6.31 (b, 1 H, minor), 5.77 (d, J =12.9 Hz, 1 H, major + minor), 5.66 (d, J =12.9 Hz, 1 H, major + minor), 4.63 (b, 1 H, major + minor), 3.95 (s, 1 H, major + minor), 3.90 (s, 3 H, major + minor), 3.81 (s, 3 H, major + minor), 2.70 (d, J =11.0 Hz, 1 H, major + minor), 2.02–0.80 (m, 14 H, major + minor), 0.94–0.83 (m, 13 H, major + minor), 0.14 (s, 3 H, major), 0.12 (s, 3 H, major), 0.09 (s, 3 H, minor), 0.07 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.61 (major), 188.56 (minor), 163.75 (major), 163.66 (minor), 162.02 (major), 161.91 (minor), 156.30 (major), 156.27 (minor), 150.24 (b, major + minor), 147.74 (major), 147.67 (minor), 133.7 (major + minor), 132.5 (major + minor), 131.9 (major + minor), 130.8 (major + minor), 129.6 (major + minor), 128.9 (major + minor), 128.5 (major + minor), 126.4 (major + minor), 125.9 (major + minor), 125.8 (major + minor),

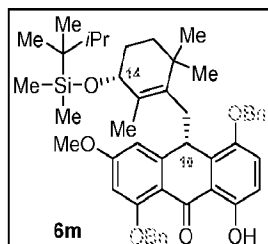
125.5 (major + minor), 123.2 (major + minor), 117.8 (major + minor), 117.77 (major), 117.74 (minor), 115.2 (major + minor), 115.1 (major + minor), 107.2 (major), 106.7 (minor), 100.1 (b, major + minor), 72.6 (b, major + minor), 69.4 (major + minor), 56.15 (minor), 56.08 (major), 55.73 (major), 55.60 (minor), 41.3 (b, major + minor), 39.0 (b, major + minor) 36.4 (b, major + minor), 36.0 (major + minor), 34.0 (major), 33.9 (minor), 29.85 (major), 29.80 (minor), 29.77 (major), 29.68 (minor), 29.13 (b, major + minor), 25.11 (major), 25.07 (minor), 20.4 (major + minor), 20.33 (major), 20.29 (minor), 18.77 (major + minor), 18.73 (major + minor), -1.72 (major), -1.82 (minor), -2.52 (major + minor) ppm; HRMS (ESI) calcd for $C_{45}H_{56}O_6SiNa^+ [M+Na]^+$ 743.3738, found 743.3739. *Due to signal broadening, not all the ^{13}C signals could be identified.



10 **(10S)-10-[(3R)-3-[(2,3-Dimethylbutan-2-yl)(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxy-1-[[4-(trifluoromethyl)benzyl]oxy]anthracen-9(10H)-one** [enantioenriched **6I**]: yellow foam, 56.2 mg, 76.0 μ mol, 76% yield, 98:2 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^{\circ}C$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.86 min for **(10R,14R)-6I**, 6.51 min for **(10S,14R)-6I**.

15 Enantioenriched **6I**: R_f =0.48 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +70.3 (c =1.0, CH_2Cl_2); FT-IR (film) ν_{max} : 2956, 2936, 2865, 1637, 1601, 1585, 1568, 1474, 1436, 1379, 1354, 1324, 1267, 1228, 1197, 1165, 1125, 1103, 1066, 1034, 1019, 1004, 934, 882, 827, 766 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, $CDCl_3$) δ 12.62 (s, 1 H, major), 12.61 (s, 1 H, minor), 7.73 (d, J =8.1 Hz, 2 H, major + minor), 7.67 (d, J =8.2 Hz, 2 H, major + minor), 7.07 (d, J =9.0 Hz, 1 H, major + minor), 6.87 (d, J =9.0 Hz, 1 H, major + minor), 6.42 (s, 1 H, major + minor), 6.40 (b, 1 H, major), 6.32 (b, 1 H, minor), 5.32 (d, J =13.1 Hz, 1 H, major + minor), 5.24 (d, J =13.1 Hz, 1 H, major + minor), 4.64 (b, 1 H, major + minor), 3.96 (b, 1 H, major + minor), 3.90 (s, 3 H, major + minor), 3.85 (s, 3 H, major + minor), 2.70 (d, J =11.7 Hz, 1 H, major + minor), 2.02–0.80 (m, 14 H, major + minor), 0.93–0.80 (m, 13 H, major + minor), 0.14 (s, 3 H, major), 0.12 (s, 3 H, major), 0.09 (s, 3 H, minor), 0.07 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, $CDCl_3$)* δ 188.66 (major), 188.61 (minor), 163.78 (major), 163.69 (minor), 161.56 (major + minor), 156.31 (major), 156.28 (minor), 150.45 (b, major + minor), 147.76 (major), 147.67 (minor), 140.8 (major + minor), 133.5 (major + minor), 130.05 (q, J =32.6 Hz, major + minor), 126.9 (major + minor), 125.70 (q, J =3.6 Hz, major + minor), 124.31 (q, J =272.3 Hz, major + minor), 117.95 (major), 117.85 (minor), 117.68 (major + minor), 115.2 (major + minor), 115.1 (major + minor), 107.3 (major), 106.7 (minor), 99.8 (major + minor), 72.6 (b, major + minor), 70.0 (major + minor), 56.13 (minor), 56.08 (major), 55.79 (major), 55.66 (minor), 41.3 (b, major + minor), 38.9 (b, major + minor) 36.3 (b, major + minor), 36.0 (major + minor), 34.0 (major), 33.9 (minor), 29.85 (major), 29.80 (minor), 29.77 (major),

29.68 (minor), 29.18 (b, major + minor), 25.11 (major), 25.06 (minor), 20.37 (major + minor), 20.31 (major + minor), 18.77 (major + minor), 18.73 (major + minor), -1.72 (major), -1.82 (minor), -2.52 (major + minor) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -61.51 ppm; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{53}\text{F}_3\text{O}_6\text{SiNa}^+ [M+\text{Na}]^+$ 761.3456, found 761.3463. *Due to signal broadening, not all the ^{13}C signals could be identified.

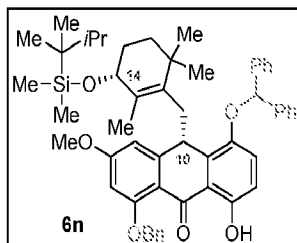


(10S)-1,5-Bis(benzyloxy)-10-[(3R)-3-[(2,3-dimethylbutan-2-yl)(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3-methoxyanthracen-9(10H)-one [enantioenriched **6m**]: yellow foam, 58.3 mg, 78.0 μmol , 78% yield, 99.0:1.0 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 $^\circ\text{C}$, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 6.27 min for (**10R,14R**)-**6m**, 7.21 min for (**10S,14R**)-**6m**.

Enantioenriched **6m**: R_f =0.55 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +61.8 (c = 1.0, CH_2Cl_2); FT-IR (film) ν_{max} : 2956, 2929, 2869, 1727, 1637, 1600, 1584, 1569, 1465, 1434, 1380, 1353, 1328, 1286, 1262, 1229, 1168, 1148, 1123, 1101, 1075, 1042, 1033, 1003, 968, 936, 883, 831, 774, 739, 696 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C-C bond; ^1H NMR (600 MHz, CDCl_3) δ 12.72 (s, 1 H, major + minor), 7.56 (d, J =7.6 Hz, 2 H, major + minor), 7.45 (d, J =7.0 Hz, 2 H, major + minor), 7.41–7.37 (m, 4 H, major + minor), 7.35 (t, J =7.5 Hz, 1 H, major + minor), 7.30 (t, J =7.4 Hz, 1 H, major + minor), 7.12 (d, J =9.0 Hz, 1 H, minor), 7.11 (d, J =9.0 Hz, 1 H, major), 6.84 (d, J =9.0 Hz, 1 H, major + minor), 6.43 (d, J =2.2 Hz, 1 H, major), 6.42 (d, J =2.2 Hz, 1 H, minor), 6.31 (b, 1 H, major), 6.21 (b, 1 H, minor), 5.25 (ABq, $\Delta\delta_{\text{AB}}$ =0.070, J =12.6 Hz, 2 H, minor), 5.11 (ABq, $\Delta\delta_{\text{AB}}$ =0.046, J =11.1 Hz, 2 H, major), 4.59 (b, 1 H, major + minor), 3.86 (b, 1 H, major + minor), 3.81 (s, 3 H, major), 3.80 (s, 3 H, minor), 2.72 (d, J =12.9 Hz, 1 H, major + minor), 2.00–0.80 (m, 14 H, major + minor), 0.93–0.80 (m, 13 H, major + minor), 0.083 (s, 3 H, major), 0.075 (s, 3 H, major), 0.07 (s, 3 H, minor), 0.05 (s, 3 H, minor) ppm; ^{13}C NMR (151 MHz, CDCl_3)* δ 188.62 (major), 188.57 (minor), 163.68 (major), 163.57 (minor), 161.98 (major + minor), 156.54 (major), 156.49 (minor), 150.03 (b, major + minor), 146.93 (major), 146.87 (minor), 136.89 (major), 136.84 (minor), 136.74 (minor), 136.71 (major), 134.1 (major + minor), 128.72 (major), 128.69 (minor), 128.67 (major), 128.65 (minor), 128.58 (major + minor), 128.39 (minor), 128.34 (major), 127.8 (major + minor), 126.79 (major), 126.77 (minor), 119.26 (major), 119.06 (minor), 117.8 (major + minor), 115.18 (major + minor), 115.14 (major + minor), 107.2 (major), 106.8 (minor), 99.98 (major + minor), 72.7 (b, major + minor), 71.73 (major), 71.66 (minor), 70.81 (major + minor), 55.71 (major), 55.55 (minor), 41.14 (b, major + minor), 38.9 (b, major + minor), 36.5 (b, major + minor), 35.85 (major), 35.78 (minor), 34.0 (major), 33.9 (minor), 31.73 (major + minor), 29.85 (major), 29.80 (minor), 29.75 (major + minor), 29.21 (b, major + minor), 25.51 (major + minor), 25.11 (major), 25.05 (minor), 22.80 (major + minor), 20.38 (major + minor), 20.29 (major + minor), 18.78 (major + minor), 18.72 (major + minor), -1.74 (major), -1.86 (minor),

−2.56 (minor), −2.61 (major) ppm; HRMS (ESI) calcd for $C_{47}H_{58}O_6SiNa^+$ $[M+Na]^+$ 769.3895, found 769.3895.

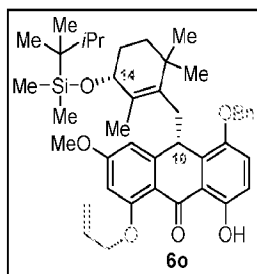
*Due to signal broadening, not all the ^{13}C signals could be identified.



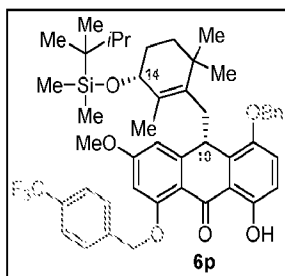
(10S)-1-(Benzyloxy)-10-[[[(3R)-3-[(2,3-dimethylbutan-2-yl)(dimethyl)silyl]oxy]-2,6,6-

5 trimethylcyclohex-1-en-1-yl]methyl]-5-(diphenylmethoxy)-8-hydroxy-3-methoxyanthracen-9(10H)-one
[enantioenriched **6n**]: yellow foam, 49.4 mg, 60.0 μ mol, 60% yield, >99:1 dr. The diastereomeric ratio was determined by HPLC after benzylation of the alkylated anthrone **6n** (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 7.41 min for benzylated **(10R,14R)-6n**, 10.39 min for benzylated **(10S,14R)-6n**.

10 Enantioenriched **6n**: R_f =0.45 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +38.2 (c =1.0, CH_2Cl_2); FT-IR (film) ν_{max} : 2956, 2926, 2866, 1726, 1636, 1599, 1583, 1569, 1468, 1433, 1379, 1352, 1327, 1287, 1254, 1228, 1206, 1197, 1168, 1121, 1100, 1076, 1042, 1033, 1022, 1002, 969, 915, 882, 831, 777, 764, 740, 697 cm^{-1} ; This compound exhibited broad NMR signals (both in ^1H NMR and ^{13}C NMR) due to hindered bond rotation of the newly-formed C–C bond; ^1H NMR (600 MHz, $CDCl_3$) δ 12.70 (s, 1 H, major + minor), 7.55 (d, J =7.5 Hz, 2 H, major + minor), 7.44 (d, J =7.2 Hz, 2 H, major + minor), 7.43–7.37 (m, 4 H, major + minor), 7.36–7.26 (m, 7 H, major + minor), 6.91 (d, J =9.1 Hz, 1 H, major + minor), 6.70 (d, J =9.0 Hz, 1 H, major + minor), 6.43 (d, J =2.1 Hz, 1 H, major), 6.43 (d, J =2.1 Hz, 1 H, minor), 6.25 (b, 1 H, major + minor), 6.21 (s, 1 H, major + minor), 5.25 (ABq, $\Delta\delta_{AB}$ =0.073, J =12.6 Hz, 2 H, major + minor), 4.59 (b, 1 H, major + minor), 3.84 (b, 1 H, major + minor), 3.80 (s, 3 H, major + minor), 2.79 (d, J =12.6 Hz, 1 H, major + minor), 2.10–0.70 (m, 14 H, major + minor), 0.95–0.85 (m, 7 H, major + minor), 0.82 (s, 6 H, major + minor), 0.07 (s, 6 H, major + minor) ppm; ^{13}C NMR (151 MHz, $CDCl_3$)* δ 188.62 (major + minor), 163.63 (major + minor), 161.92 (major + minor), 156.56 (major + minor), 156.52 (major + minor), 146.34 (major + minor), 140.73 (b, major + minor), 140.61 (major + minor), 136.7 (major + minor), 134.3 (major + minor), 128.8 (major + minor), 128.72 (major + minor), 128.66 (major + minor), 128.6 (major + minor), 128.1 (major + minor), 128.0 (major + minor), 127.9 (major + minor), 127.8 (major + minor), 127.7 (major + minor), 126.79 (major + minor), 126.76 (major + minor), 120.9 (major + minor), 117.76 (minor), 117.73 (major), 115.2 (major + minor), 107.2 (major + minor), 100.04 (major + minor), 83.7 (major + minor), 70.8 (major + minor), 55.7 (major + minor), 35.8 (major + minor), 35.7 (major + minor), 34.0 (major + minor), 29.9 (major + minor), 29.8 (major + minor), 29.5 (major + minor), 25.1 (major), 25.0 (minor), 20.4 (major + minor), 20.3 (major + minor), 18.8 (major + minor), 18.7 (major + minor), −1.7 (major + minor), −2.6 (major + minor) ppm; HRMS (ESI) calcd for $C_{53}H_{62}O_6SiNa^+$ $[M+Na]^+$ 845.4208, found 845.4208. *Due to signal broadening, not all the ^{13}C signals could be identified.



(10*S*)-1-(Allyloxy)-5-(benzyloxy)-10-[[[(3*R*)-3-[[[2,3-dimethylbutan-2-yl](dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3-methoxyanthracen-9(10*H*)-one [enantioenriched **6o**]: yellow foam, 51.6 mg, 74.0 μ mol, 74% yield, 99:1 dr. The diastereomeric ratio was determined by HPLC after benzylation of the alkylated anthrone **6o** (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 7.06 min for benzylated (**10*R*,14*R***)-**6o**, 9.75 min for benzylated (**10*S*,14*R***)-**6o**. Enantioenriched **6o**: R_f =0.52 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +66.9 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2956, 2925, 2868, 1726, 1637, 1599, 1583, 1568, 1464, 1435, 1377, 1353, 1326, 1283, 1261, 1227, 1197, 1169, 1119, 1096, 1074, 1041, 1027, 1001, 981, 967, 934, 882, 830, 775, 739, 696, 667 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR) due to hindered bond rotation of the newly-formed C–C bond; ¹H NMR (600 MHz, CDCl₃) δ 12.65 (s, 1 H, major + minor), 7.44 (d, J =6.9 Hz, 2 H, major + minor), 7.38 (ap t, J =7.2 Hz, 2 H, major + minor), 7.34 (ap t, J =7.2 Hz, 1 H, major + minor), 7.10 (d, J =9.0 Hz, 1 H, major + minor), 6.82 (d, J =9.0 Hz, 1 H, major + minor), 6.40 (d, J =2.1 Hz, 1 H, major), 6.38 (d, J =2.1 Hz, 1 H, minor), 6.31 (b, 1 H, major), 6.21 (b, 1 H, minor), 6.10 (ap ddt, J =17.2, 10.5, 4.7 Hz, 1 H, major + minor), 5.63 (dd, J =17.2, 1.5 Hz, 1 H, major + minor), 5.35 (dd, J =10.7, 1.5 Hz, 1 H, major + minor), 5.10 (dd, J =18.2, 11.1 Hz, 2 H, major + minor), 4.63 (ddd, J =13.4, 7.3, 5.2 Hz, 2 H, major + minor), 4.60 (b, 1 H, major + minor), 3.87 (b, 1 H, major + minor), 3.84 (s, 3 H, major), 3.83 (s, 3 H, minor), 2.71 (d, J =12.2 Hz, 1 H, major + minor), 1.99–0.65 (m, 14 H, major + minor), 0.95–0.85 (m, 7 H, major + minor), 0.82 (s, 6 H, major), 0.72 (s, 6 H, minor), 0.09 (s, 6 H, major), 0.07 (s, 6 H, minor) ppm; ¹³C NMR (151 MHz, CDCl₃)* δ 188.61 (major + minor), 171.28 (major + minor), 163.73 (major + minor), 162.07 (major + minor), 156.50 (major + minor), 150.06 (b, major + minor), 146.91 (major + minor), 136.9 (major + minor), 134.1 (major + minor), 132.5 (major + minor), 128.7 (major + minor), 128.6 (major + minor), 128.3 (major + minor), 119.2 (major + minor), 117.9 (major + minor), 117.8 (major + minor), 115.2 (major + minor), 115.0 (major + minor), 106.9 (major + minor), 99.6 (major + minor), 72.7 (b, major + minor), 71.7 (major + minor), 69.8 (major + minor), 60.5 (major + minor), 55.7 (major + minor), 41.1 (b, major + minor), 39.0 (b, major + minor), 36.5 (b, major + minor), 35.85 (major), 35.77 (minor), 34.0 (major + minor), 29.84 (major + minor), 29.75 (major + minor), 29.2 (major + minor), 25.1 (major), 25.0 (minor), 20.4 (major + minor), 20.3 (major + minor), 18.8 (major + minor), 18.7 (major + minor), 14.3 (major + minor), -1.7 (major + minor), -2.6 (major + minor) ppm; HRMS (ESI) calcd for C₄₃H₃₆O₆SiNa⁺ [M +Na]⁺ 719.3738, found 719.3734. *Due to signal broadening, not all the ¹³C signals could be identified.



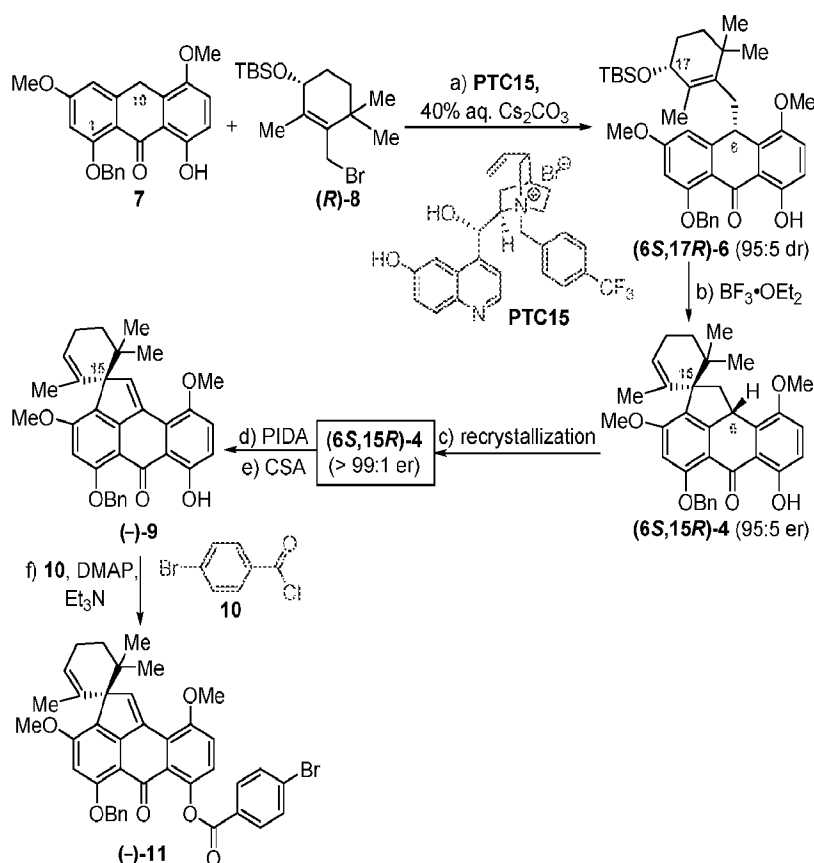
(10S)-5-(Benzyloxy)-10-[[[(3R)-3-[(2,3-dimethylbutan-2-yl)(dimethyl)silyloxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3-methoxy-1-[[4-

(trifluoromethyl)benzyl]oxy]anthracen-9(10H)-one [enantioenriched **6p**]: yellow foam, 61.1 mg, 75.0 μ mol,

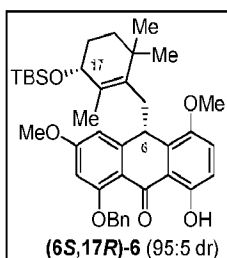
- 75% yield, > 99:1 dr. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.79 min for **(10R,14R)-6p**, 6.45 min for **(10S,14R)-6p**. Enantioenriched **6p**: R_f =0.60 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{22}$ = +48.0 (c =1.0, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2957, 2927, 2869, 1727, 1637, 1601, 1584, 1568, 1465, 1435, 1379, 1353, 1325, 1286, 1265, 1229, 1197, 1166, 1125, 1102, 1067, 1042, 1033, 1022, 1004, 969, 936, 882, 830, 775, 741, 696, 670 cm⁻¹; This compound exhibited broad NMR signals (both in ¹H NMR and ¹³C NMR) due to hindered bond rotation of the newly-formed C–C bond; ¹H NMR (600 MHz, CDCl₃) δ 12.65 (s, 1 H, major + minor), 7.70 (dd, J =36.9, 8.2 Hz, 4 H, major + minor), 7.48–7.32 (m, 5 H), 7.12 (d, J =9.0 Hz, 1 H, major + minor), 6.85 (d, J =9.0 Hz, 1 H, major + minor), 6.41 (d, J =2.1 Hz, 1 H, major), 6.39 (d, J =2.1 Hz, 1 H, minor), 6.34 (b, 1 H, major), 6.24 (b, 1 H, minor), 5.28 (ABq, $\Delta\delta_{AB}$ =0.082, J =13.1 Hz, 2 H, minor), 5.11 (ABq, $\Delta\delta_{AB}$ =0.048, J =11.1 Hz, 2 H, major), 4.62 (b, 1 H, major + minor), 3.87 (b, 1 H, major + minor), 3.83 (s, 3 H, major), 3.81 (s, 3 H, minor), 2.73 (d, J =12.3 Hz, 1 H, major + minor), 1.95–0.60 (m, 14 H, major + minor), 0.95–0.87 (m, 7 H, major + minor), 0.84 (s, 6 H, major), 0.80 (s, 6 H, minor), 0.08 (s, 3 H, major + minor), 0.07 (s, 3 H, major), 0.06 (s, 6 H, minor) ppm; ¹³C NMR (151 MHz, CDCl₃)* δ 188.65 (major + minor), 163.7 (major + minor), 161.5 (major + minor), 156.6 (major + minor), 147.0 (major + minor), 140.8 (major + minor), 136.8 (major + minor), 134.1 (major + minor), 130.05 (q, J =32.4 Hz, major + minor), 128.7 (major + minor), 128.6 (major + minor), 128.4 (major + minor), 126.9 (major + minor), 125.71 (q, J =3.5 Hz), 124.31 (q, J =271.8 Hz), 119.4 (major + minor), 117.7 (major + minor), 115.3 (major + minor), 115.1 (major + minor), 107.3 (major + minor), 99.9 (major + minor), 71.7 (major + minor), 70.0 (major + minor), 56.1 (major + minor), 55.8 (major + minor), 41.1 (b, major + minor), 36.5 (b, major + minor), 35.9 (major + minor), 34.0 (major + minor), 29.9 (major + minor), 29.8 (major + minor), 25.1 (major + minor), 20.4 (major + minor), 20.3 (major + minor), 18.8 (major + minor), 18.7 (major + minor), 14.3 (major + minor), -1.7 (major + minor), -2.6 (major + minor) ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ -61.51 ppm; HRMS (ESI) calcd for C₄₈H₅₇O₆SiNa⁺ [M +Na]⁺ 837.3769, found 837.3768. *Due to signal broadening, not all the ¹³C signals could be identified.

Enantioselective Total Synthesis and Absolute Configuration of (–)-Viridicatumtoxin B

Scheme 14. Enantioselective Synthesis of the BCDEF Fragment (6*S*,15*R*)-4 of (–)-Viridicatumtoxin B [(–)-1] and Its Absolute Configuration

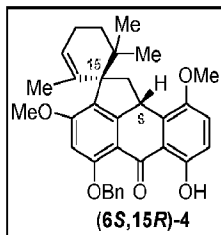


Note: to avoid confusion, the numbering on **(6*S*,17*R*)-6**, **(6*S*,15*R*)-4** and **(–)-9** in this Scheme is based on the viridicatumtoxin numbering, as opposed to the carbon numbering of compound **(10*S*,14*R*)-6** (see Table 3), which is the same compound as **(6*S*,17*R*)-6**, but numbered based on the anthrone numbering.



(10*S*)-1-(Benzyloxy)-10-[[[(3*R*)-3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10*H*)-one [(6*S*,17*R*)-6]: To a stirred mixture of anthrone **7** (3.01 g, 8.00 mmol, 1.0 equiv), allylic bromide **(R)-8** (3.06 g, 8.80 mmol, 1.1 equiv) and **PTC15** (22.0 mg, 40.0 μmol , 0.5 mol%, 0.005 equiv) in $(\text{CH}_2)_2\text{Cl}_2$ (80 mL) under argon, was added 50% aq. KOH solution (24 mL) dropwise at -30°C . The reaction mixture was stirred vigorously at -30°C for 240 h (10 days). The mixture was then quenched by addition of water (150 mL) and extracted with CH_2Cl_2 ($3 \times 150\text{ mL}$). The organic phase was washed with brine (100 mL) and dried over anhydrous Na_2SO_4 . Evaporation of solvents and purification of the residue by flash column chromatography on silica gel (10% EtOAc:hexanes) gave chiral alkylated anthrone **(6*S*,17*R*)-6** (3.70 g, 5.76 mmol, 72% yield, 95:5 dr) as a yellow foam. Compound **(6*S*,17*R*)-6** is the same as

(10*S*,14*R*)-6, which is numbered based on the viridicatumtoxin numbering. The diastereomeric ratio was determined by HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 7.01 min for (6*R*,17*R*)-6; 8.05 min for (6*S*,17*R*)-6. The physical and spectroscopic data of this compound matched those mentioned above of (10*S*,14*R*)-6.



5

(2*R*,10*bS*)-5-(Benzyloxy)-7-hydroxy-3,10-dimethoxy-2',6',6'-trimethyl-1,10*b*-dihydro-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]en]-6-one [(6*S*,15*R*)-4]: Chiral alkylated anthrone (6*S*,17*R*)-6 (3.70 g, 5.76 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (360 mL) and cooled to -78 °C. A freshly prepared solution of BF₃·Et₂O (2.90 mL of a 0.1 M solution in CH₂Cl₂, 290 μmol, 0.05 equiv) was added dropwise, and the reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 0.5 h. The reaction was quenched by addition saturated aq. NaHCO₃ solution (200 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (200 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5%→10% EtOAc:hexanes) to give chiral *BCDEF* spirocycle (6*S*,15*R*)-4 (2.18 g, 4.26 mmol, 74% yield, 95:5 er) as a yellow foam. The enantiomeric ratio was determined by HPLC (Chiralcel OD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 6.56 min for (6*R*,15*S*)-4; 7.78 min for (6*S*,15*R*)-4.

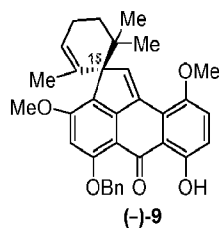
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After recrystallization from hexanes:CH₂Cl₂ (50:1), yellow crystals were obtained with 99.2:0.8 er (91% yield). (6*S*,15*R*)-4: R_f=0.50 (silica gel, EtOAc:hexanes 1:4); [α]_D²² = +65.7 (*c*=1.0, CH₂Cl₂, 99.2:0.8 er); m.p. = 157–158 °C [dec., hexanes:CH₂Cl₂ 50:1]; FT-IR (film) ν_{max}: 2939, 2917, 2838, 1633, 1598, 1568, 1472, 1441, 1383, 1328, 1301, 1270, 1257, 1220, 1200, 1139, 1106, 1034, 1001, 924, 867, 824, 790, 770, 735, 705, 696 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 13.14 (s, 1 H), 7.60 (d, *J*=7.4 Hz, 2 H), 7.42 (ap t, *J*=7.6 Hz, 2 H), 7.33 (ap t, *J*=7.4 Hz, 1 H), 7.06 (d, *J*=9.0 Hz, 1 H), 6.86 (d, *J*=9.0 Hz, 1 H), 6.40 (s, 1 H), 5.43 (d, *J*=3.5 Hz, 1 H), 5.37 (d, *J*=12.4 Hz, 1 H), 5.28 (d, *J*=12.4 Hz, 1 H), 4.40 (dd, *J*=11.8, 7.5 Hz, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.14 (dd, *J*=13.7, 7.5 Hz, 1 H), 2.26–2.15 (m, 2 H), 2.02 (dd, *J*=14.3, 8.9 Hz, 1 H), 1.95 (ap td, *J*=12.5, 6.1 Hz, 1 H), 1.38 (dd, *J*=13.1, 6.0 Hz, 1 H), 1.27 (s, 3 H), 1.00 (s, 3 H), 0.96 (s, 3 H), 0.92 (s, 1 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 189.0, 162.1, 161.2, 157.4, 155.4, 149.3, 138.3, 136.9, 131.1, 128.8, 128.0, 127.0, 124.1, 121.3, 119.3, 118.1, 115.7, 112.8, 97.0, 71.6, 58.8, 56.6, 55.2, 44.9, 41.7, 38.8, 34.9, 27.8, 25.8, 24.9, 23.1, 20.5 ppm; HRMS (ESI) calcd for C₃₃H₃₄O₅Na⁺ [*M*+Na]⁺ 533.2298, found 533.2304.

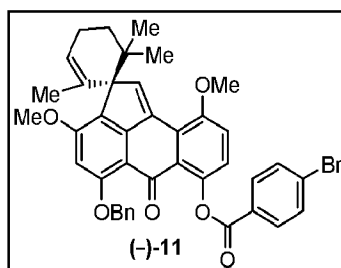
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(2*R*)-5-(Benzyloxy)-7-hydroxy-3,10-dimethoxy-2',6',6'-trimethyl-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]en]-6-one [(-)-9] (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Spirocyclic (6*S*,15*R*)-4 (2.00 g, 3.92 mmol, 1.0 equiv) was dissolved in MeOH:CH₂Cl₂ (1:1, 80 mL), and the solution was cooled to 0 °C. Freshly prepared PhI(OAc)₂³⁷ (1.51 g, 4.69 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 30 min at 0 °C and 30 min at 25 °C. The reaction was quenched by addition of saturated aq. NaHCO₃ (200 mL) and was extracted with EtOAc (2 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The so-obtained crude ketal was dissolved in CH₂Cl₂ (80 mL), and freshly crystallized CSA (63.0 mg, 270 μmol, 0.07 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C for 5 minutes and was then quenched by addition of saturated aq. NaHCO₃ (100 mL). The layers were separated, and the organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude product (-)-9. Flash column chromatography (silica gel, 2% EtOAc:toluene) gave intermediate (-)-9 (1.61 g, 3.16 mmol, 81% for two steps, > 99:1 er) as a red solid. The enantiomeric ratio was determined by HPLC (Chiralcel OD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 8.63 min for (-)-9 [(15*S*)-9], 9.14 min for (+)-9 [(15*R*)-9].

(-)-9: *R*_f=0.70 (silica gel, EtOAc:hexanes 1:9); [α]_D²² = -130 (*c*=0.05, CH₂Cl₂); m.p. = 199–200 °C (CH₂Cl₂); FT-IR (film) ν_{max} : 2936, 2324, 2162, 2050, 1981, 1625, 1574, 1479, 1442, 1429, 1384, 1363, 1331, 1311, 1259, 1238, 1222, 1180, 1163, 1128, 1029, 931, 874, 829, 806, 735, 716, 696 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 13.98 (s, 1 H), 7.65–7.63 (m, 2 H), 7.60 (s, 1 H), 7.45–7.41 (m, 2 H), 7.34 (m, 1 H), 7.20 (d, *J*=6.0 Hz, 1 H), 7.00 (d, *J*=6.0 Hz, 1 H), 6.44 (s, 1 H), 5.74 (bs, 1 H), 5.38 (d, *J*=12.8 Hz, 1 H, AB system), 5.35 (d, *J*=12.8 Hz, 1 H, AB system), 3.97 (s, 3 H), 3.81 (s, 3 H), 2.31–2.22 (m, 2 H), 1.90 (ddd, *J*=12.9, 5.6, 5.6 Hz, 1 H), 1.66 (ddd, *J*=12.9, 6.5, 6.5 Hz, 1 H), 1.14 (s, 3 H), 0.85 (s, 6 H) ppm; ¹³C NMR (CDCl₃, 151 MHz) δ 188.5, 161.2, 159.8, 157.9, 152.4, 151.6, 150.4, 136.9, 131.7, 130.6, 128.8, 128.0, 126.9, 124.6, 124.1, 120.2, 118.1, 117.4, 116.8, 110.3, 96.0, 71.4, 66.9, 56.2, 55.5, 37.0, 35.8, 27.1, 26.8, 23.2, 19.8 ppm; HRMS (ESI) calcd for C₃₃H₃₂O₅Na⁺ [*M*+Na]⁺ 531.2142, found 531.2146.

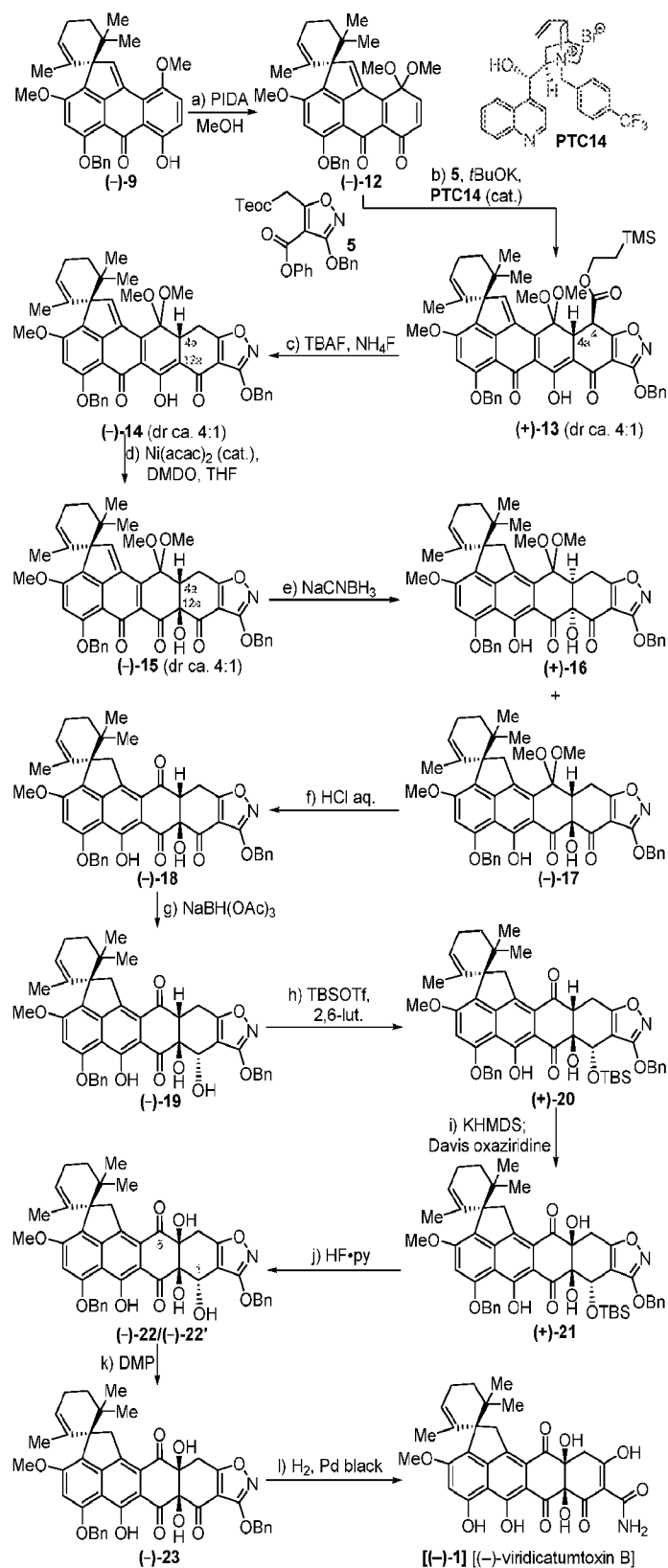


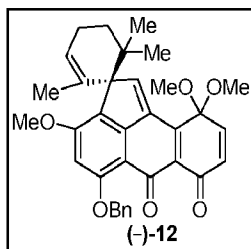
(2*R*)-5-(Benzyloxy)-3,10-dimethoxy-2',6',6'-trimethyl-6-oxo-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]en]-7-yl 4-bromobenzoate (-)-11: To a stirred solution of quinomethide (-)-9 (15.3 mg, 30.0 μmol,

1.0equiv) in CH₂Cl₂ (2 mL) was added 4-bromobenzoyl chloride **10** (32.9 mg, 150 μmol, 5equiv), 4-dimethylaminopyridine (DMAP, 36.7 mg, 300 μmol, 10equiv) and triethylamine (Et₃N, 126 μL, 91.1 mg, 900 μmol, 30equiv). The reaction mixture was stirred at 25 °C for 6 h before the reaction was quenched by addition of saturated aq. NaHCO₃ solution (5 mL) and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic
5 phases were dried over Na₂SO₄, and concentrated under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc:hexanes) gave protected *p*-bromobenzoate (–)-**11** (19.7 mg, 28.5 μmol, 95% yield) as a yellow solid. Crystallization from CH₂Cl₂/hexanes 1:4 gave crystals suitable for X-ray crystallographic analysis, which revealed its absolute configuration as shown below (FIG. 4).

(–)-**11**: R_f=0.60 (silica gel, EtOAc:hexanes 1:9); [α]_D²² = –87 (c=0.1, CH₂Cl₂); m.p.=220–221 °C
10 (CH₂Cl₂/hexanes 1:4); FT-IR (film) ν_{max}: 2960, 2923, 2854, 1736, 1647, 1616, 1581, 1497, 1484, 1462, 1442, 1423, 1396, 1384, 1361, 1332, 1273, 1240, 1222, 1172, 1142, 1123, 1075, 1021, 1011, 918, 871, 843, 807, 775, 741, 697, 676 cm^{–1}; ¹H NMR (600 MHz, CDCl₃) δ 8.21 (d, *J*=8.4 Hz, 2H), 7.69 (d, *J*=8.4 Hz, 2H), 7.61 (s, 1H), 7.46 (d, *J*=7.5 Hz, 2H), 7.28–7.24 (m, 1H), 7.22–7.15 (m, 4H), 6.42 (s, 1H), 5.75–5.73 (m, 1H), 5.17–5.12 (m, 2H), 4.05 (s, 3H), 3.83 (s, 3H), 2.30–2.26 (m, 2H), 1.95–1.88 (m, 1H), 1.71–1.64 (m, 1H), 1.16 (d, *J*=1.0 Hz, 3H), 0.86 (s, 6H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 181.0, 166.1, 160.6, 159.1, 156.3, 152.2,
150.5, 144.7, 137.1, 132.4, 131.9, 131.8, 130.1, 130.0, 128.4, 128.1, 127.6, 126.9, 125.5, 124.4, 124.0, 123.8, 122.8, 113.8, 112.2, 97.1, 71.6, 66.8, 56.1, 55.5, 37.0, 35.9, 27.1, 26.8, 23.3, 19.9 ppm; HRMS (ESI) calcd for C₄₀H₃₅BrO₆Na⁺ [*M*+Na]⁺ 713.1509, found 713.1511.

Scheme 15. Total Synthesis of Enantiopure (–)-Viridicatumtoxin B [(–)-1]



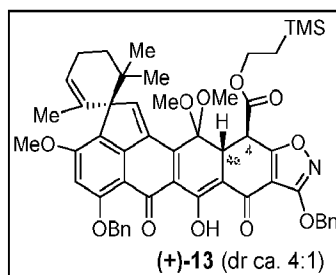


(2*R*)-5-(Benzyloxy)-3,10,10-trimethoxy-2',6',6'-trimethyl-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]ene]-6,7(10*H*)-dione (-)-12 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Quinomethide (-)-9 (1.31 g, 2.55 mmol, 1.0 equiv) was dissolved in a mixture of CH₂Cl₂:MeOH (1:10; 55 mL), and freshly prepared

5 PhI(OAc)₂ (Sharefkin and Saltzman., 1963) (1.00 g, 3.10 mmol, 1.2 equiv) was added with stirring at 25 °C. The reaction mixture was stirred at that temperature for 1.5 h and was then quenched by addition of saturated aq. NaHCO₃ (50 mL). The resulting mixture was diluted with water (100 mL) and extracted with CH₂Cl₂ (100 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 10% acetone in toluene, 0.1% Et₃N) to give diketone

10 ketal (-)-12 (1.19 g, 2.20 mmol, 86% yield) as a yellow solid. (-)-12: R_f=0.15 (silica gel, acetone:toluene 1:9); [α]_D²² = -132 (*c*=0.1, CH₂Cl₂); m.p. = 194–195 °C (dec., CH₂Cl₂); FT-IR (film) ν_{max}: 2937, 2835, 1681, 1618, 1582, 1456, 1435, 1373, 1328, 1282, 1224, 1094, 1082, 1067, 846, 733 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 7.83 (s, 1 H), 7.65–7.62 (m, 2 H), 7.43–7.39 (m, 2 H), 7.32 (m, 1 H), 6.64 (d, *J*=10.4 Hz, 1 H), 6.59 (d, *J*=10.4 Hz, 1 H), 6.43 (s, 1 H), 5.76 (bs, 1 H), 5.30 (d, *J*=12.0 Hz, 1 H, AB system), 5.26 (d, *J*=12.0 Hz, 1 H, AB system),

15 3.82 (s, 3 H), 3.26 (s, 3 H), 3.17 (s, 3 H), 2.28–2.23 (m, 2 H), 1.94 (ddd, *J*=13.1, 6.3, 6.3 Hz, 1 H), 1.61 (m, 1 H), 1.13 (bs, 3 H), 0.88 (s, 3 H), 0.82 (s, 3 H) ppm; ¹³C NMR (CDCl₃, 151 MHz) δ 183.3, 179.6, 161.6, 160.6, 159.2, 148.4, 147.1, 140.9, 136.7, 135.2, 130.5, 130.1, 130.0, 128.7, 127.9, 127.1, 125.0, 123.5, 112.2, 96.7, 96.5, 71.1, 68.6, 56.0, 51.7, 51.6, 37.5, 35.5, 27.1, 26.9, 23.1, 19.9 ppm; HRMS (ESI) calcd for C₃₄H₃₄O₆Na⁺ [*M*+Na]⁺ 561.2248, found 561.2249.



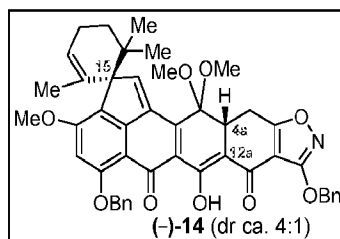
20

2-(Trimethylsilyl)ethyl (1*R*,12'*R*,12*a*'*R*)-5',9'-bis(benzyloxy)-7'-hydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-6',8'-dioxo-8',12',12*a*',13'-tetrahydro-6'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-12'-carboxylate (+)-13 (ca. 4:1 mixture of C15–C4/C4*a* diastereomers): To a stirred solution of pentacycle 12 (1.00 g, 1.84 mmol, 1.0 equiv), potassium *tert*-butoxide

25 (*t*BuOK, 248 mg, 2.24 mmol, 1.2 equiv) and PTC-14 (9.80 mg, 18.4 μmol, 0.01 equiv) in toluene (18 mL) at -78 °C under argon was added dropwise a solution of phenyl ester isoxazole 5 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014) (920 mg, 2.04 mmol, 1.1 equiv) in toluene (18 mL). The resulting solution was then warmed to -50 °C and stirred at that temperature for 48 h. Then, the reaction was quenched by addition of saturated aq.

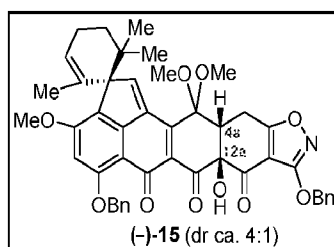
NH₄Cl solution (40 mL). The phases were separated, and the organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 2%→5% acetone in toluene) to give product **13** (1.47 g, 1.62 mmol, 88% yield, dr ca. 4:1) as a yellow foam.

13: R_f=0.60 (silica gel, EtOAc:hexanes 3:7); [α]_D²² = +153 (*c*=0.1, CH₂Cl₂); FT-IR (film) $\nu_{\max}$: 2952, 1737, 1656, 1618, 1582, 1511, 1489, 1454, 1385, 1366, 1308, 1250, 1223, 1157, 1054, 1025, 932, 859, 838, 736, 696 cm⁻¹; ¹H NMR (C₆D₆, 600 MHz) δ 16.73 (bs, 1 H, major + minor), 7.70–7.64 (m, 2 H, major + minor), 7.61 (s, 1 H, minor), 7.58 (s, 1 H, major), 7.39–7.35 (m, 2 H, major + minor), 7.21–7.02 (m, 6 H, major + minor), 6.24 (bs, 1 H, minor), 6.23 (bs, 1 H, major), 5.72 (bs, 1 H, minor), 5.69 (bs, 1 H, major), 5.19–5.17 (m, 2 H, major + minor), 5.06–5.01 (m, 2 H, major + minor), 4.73 (d, *J*=10.0 Hz, 1 H, major), 4.72 (m, 1 H, minor), 4.42–4.26 (m, 2 H, major + minor), 4.22 (d, *J*=10.0 Hz, 1 H, major), 4.20 (d, *J*=10.0 Hz, 1 H, minor), 3.23 (s, 3 H, major), 3.22 (s, 3 H, minor), 3.13 (s, 3 H, major), 3.09 (s, 3 H, minor), 3.03 (s, 3 H, minor), 2.97 (s, 3 H, major), 2.26–2.18 (m, 1 H, major + minor), 2.14–2.07 (m, 1 H, major + minor), 1.96 (ddd, *J*=13.2, 6.6, 6.6 Hz, 1 H, major), 1.89 (ddd, *J*=13.2, 6.7, 6.7 Hz, 1 H, minor), 1.47 (ap ddd, *J*=13.2, 6.7, 6.7 Hz, 2 H, major + minor), 1.23 (bs, 3 H, minor), 1.17 (bs, 3 H, major), 1.01 (ap t, *J*=8.5 Hz, 2 H, major + minor), 0.99 (ap t, *J*=8.5 Hz, 2 H, major + minor), 0.91 (s, 3 H, major), 0.90 (s, 3 H, minor), 0.87 (s, 3 H, major), 0.82 (s, 3 H, minor), –0.09 (s, 9 H, major), –0.11 (s, 9 H, minor) ppm; ¹³C NMR (C₆D₆, 151 MHz) δ 181.4 (major), 181.3 (minor), 178.8 (major), 178.4 (minor), 175.5 (major), 175.4 (minor), 171.6 (minor), 171.5 (major), 169.2 (major), 169.1 (minor), 168.4 (major + minor), 161.0 (minor), 160.5 (major), 159.2 (minor), 159.0 (major), 157.4 (major), 157.3 (minor), 148.7 (minor), 148.5 (major), 140.13 (minor), 140.06 (major), 137.40 (minor), 137.35 (major), 135.9 (major + minor), 134.8 (minor), 134.7 (major), 132.5 (major), 132.4 (minor), 130.7 (minor), 130.6 (major), 128.9 (major + minor)*, 128.7 (major)*, 128.6 (minor)*, 128.56 (minor)*, 128.47 (major)*, 127.32 (minor), 127.25 (major), 125.15 (minor), 125.12 (major), 123.5 (minor), 123.3 (major), 113.3 (major), 113.2 (minor), 106.3 (major + minor), 103.29 (major), 103.26 (minor), 102.6 (major), 102.5 (minor), 97.8 (minor), 97.4 (major), 72.3 (major + minor), 71.6 (minor), 71.4 (major), 68.40 (minor), 68.35 (major), 64.8 (major + minor), 54.98 (major + minor), 54.2 (major), 53.7 (minor), 52.8 (minor), 52.5 (major), 40.69 (minor), 40.65 (major), 40.2 (major + minor), 37.7 (major), 37.5 (minor), 35.8 (major + minor), 27.21 (major), 27.14 (minor), 27.14 (minor), 27.06 (major), 23.4 (major + minor), 20.3 (minor), 20.2 (major), 17.4 (major + minor), –1.66 (major), –1.67 (minor) ppm; HRMS (ESI) calcd for C₅₂H₅₅NO₁₁SiNa⁺ [*M*+Na]⁺ 920.3437, found 920.3428. *Due to overlapping ¹³C chemical shifts of diastereomers, these signals could not be assigned with accuracy.

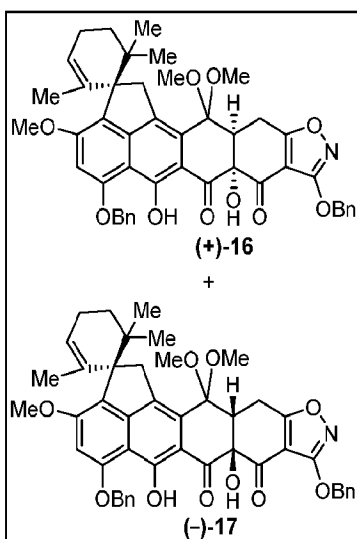


(1*R*,12*a'**R*)-5',9'-Bis(benzyloxy)-7'-hydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a'*,13'-dihydro-6'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-6',8'(12'*H*)-dione (–)-**14** (ca. 4:1 mixture of C15–C4*a* diastereomers) [Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014]: A solution of

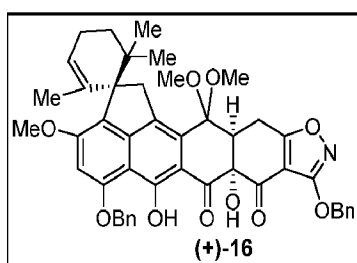
Teoc-heptacycle (+)-**13** (1.60 g, 1.80 mmol, 1.0 equiv, dr ca. 4:1) and NH_4F (1.35 g, 35.5 mmol, 20 equiv) in THF (200 mL) was degassed three times with argon at -78°C , and the reaction flask was shielded from light using aluminum foil. A freshly prepared solution of tetra-*n*-butylammonium fluoride (18.0 mL, 1 M solution in THF, 18.0 mmol, 10 equiv, prepared from $\text{TBAF} \cdot 3\text{H}_2\text{O}$) was added in one portion at -78°C . The reaction mixture was warmed to 25°C and stirred for 10 minutes. The reaction was then quenched by addition of brine (120 mL) and extracted with EtOAc (120 mL). The layers were separated, and the organic phase was washed with water ($3 \times 100\text{ mL}$), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 2% $\rightarrow$ 5% acetone in toluene) to give heptacycle (–)-**14** (1.17 g, 1.57 mmol, 87% yield, dr ca. 4:1) as an orange foam. (–)-**14**: $R_f=0.50$ (silica gel, acetone:toluene 1:9); $[\alpha]_D^{22}=-24$ ($c=0.05$, CH_2Cl_2); FT-IR (film) ν_{max} : 2956, 2927, 2855, 1711, 1653, 1618, 1582, 1509, 1455, 1365, 1311, 1258, 1219, 1157, 1075, 1052, 1027, 912, 814, 736, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 15.60 (s, 1 H, major), 15.59 (s, 1 H, minor), 7.72 (s, 1 H, major), 7.70 (s, 1 H, minor), 7.61–7.57 (m, 2 H, major + minor), 7.52–7.49 (m, 2 H, major + minor), 7.41–7.36 (m, 4 H, major + minor), 7.35–7.29 (m, 2 H, major + minor), 6.45 (s, 1 H, minor), 6.44 (s, 1 H, major), 5.77 (bs, 1 H, minor), 5.76 (bs, 1 H, major), 5.40 (s, 2 H, major + minor), 5.35–5.25 (m, 2 H, major + minor), 3.91 (dd, $J=11.0, 8.3\text{ Hz}$, 1 H, major), 3.86 (dd, $J=11.0, 8.5\text{ Hz}$, 1 H, minor), 3.80 (s, 3 H, minor), 3.79 (s, 3 H, major), 3.45 (s, 3 H, major), 3.40 (s, 3 H, minor), 3.44–3.43 (m, 1 H, minor), 3.41–3.39 (m, 1 H, major), 3.34 (s, 3 H, minor), 3.27 (s, 3 H, major), 3.02–2.94 (m, 2 H, major + minor), 2.26 (bs, 2 H, major + minor), 1.99 (ap dt, $J=13.2, 6.5\text{ Hz}$, 1 H, major + minor), 1.62 (bs, 1 H, major + minor), 1.55 (ap dt, $J=12.9, 6.3\text{ Hz}$, 1 H, major + minor), 1.13 (s, 3 H, minor), 1.09 (s, 3 H, major), 0.93 (s, 3 H, major), 0.88 (s, 3 H, minor), 0.79 (s, 3 H, major), 0.77 (s, 3 H, minor) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 182.1 (major), 182.0 (minor), 180.1 (major), 179.8 (minor), 179.1 (major + minor), 170.0 (major + minor), 168.1 (major + minor), 160.7 (minor), 160.3 (major), 159.41 (major), 159.37 (minor), 159.2 (minor), 159.1 (major), 148.2 (minor), 148.1 (major), 141.17 (minor), 141.15 (major), 136.80 (major + minor), 135.46 (major + minor), 132.84 (major + minor), 132.61 (major), 132.56 (minor), 130.0 (major + minor), 128.8 (major + minor)*, 128.7 (major + minor)*, 128.6 (major + minor)*, 128.41 (major)*, 128.35 (minor)*, 127.9 (major + minor)*, 127.2 (minor), 127.1 (major), 125.4 (minor), 125.2 (major), 123.4 (minor), 123.2 (major), 112.3 (major), 112.2 (minor), 105.7 (major + minor), 103.43 (major), 103.38 (minor), 102.17 (major), 102.15 (minor), 97.2 (minor), 97.0 (major), 72.4 (major + minor), 71.40 (minor), 71.36 (major), 68.4 (minor), 68.3 (major), 55.6 (minor), 55.5 (major), 53.5 (major), 53.0 (minor), 52.9 (minor), 52.6 (major), 37.8 (major), 37.6 (minor), 37.0 (minor), 36.9 (major), 35.64 (major), 35.60 (minor), 27.3 (minor), 27.2 (major), 26.9 (minor), 26.8 (major), 23.12 (major + minor), 20.5 (major + minor), 20.0 (major + minor) ppm; HRMS (ESI) calcd for $\text{C}_{46}\text{H}_{43}\text{NO}_9\text{Na}^+ [M+\text{Na}]^+$ 776.2830, found 776.2857. *Due to overlapping ^{13}C chemical shifts of diastereomers, these signals could not be assigned with accuracy.



(1*R*,7*a*'*S*,12*a*'*R*)-5',9'-Bis(benzyloxy)-7*a*'-hydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-6'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-6',7',8'(7*a*'*H*,12'*H*)-trione (–)-**15** (ca 4:1 mixture of C15–C4*a*/C12*a* diastereomers): To a stirred solution of substrate (–)-**14** (250 mg, 330 μ mol, 1.0 equiv, dr ca. 4:1) in THF (25 mL) under argon was added a solution of Ni(acac)₂ (17.0 mg, 66.0 μ mol, 0.20 equiv) in THF (2 mL), stirred for five minutes at 25 °C, and then cooled to –78 °C. DMDO³⁸ (~0.08 M solution in acetone, 13.0 mL, ~0.990 mmol, 3.0 equiv) was added dropwise at –78 °C and further stirred at this temperature for 3 h. The reaction was then quenched by addition of dimethylsulfide (1.0 mL), and the mixture was stirred at –78 °C for 15 minutes. Saturated aq. NH₄Cl solution (15 mL) was added, and the mixture was allowed to warm to 25 °C and then diluted with water (20 mL) and extracted with EtOAc (3 $\times$ 20 mL). The layers were separated, and the organic phase was washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% $\rightarrow$ 5% $\rightarrow$ 10% acetone in toluene) gave the hydroxylated product (–)-**15** (131 mg, 172 μ mol, 52% yield, 72% yield brsm, dr ca. 4:1) as an orange powder and recovered starting material (–)-**14** (70.2 mg, 92.9 μ mol, 28% yield). **15**: R_f = 0.25 (silica gel, acetone:toluene 1:9); [α]_D²² = –116 (*c* = 0.2, CH₂Cl₂); FT-IR (film) ν_{max} : 3425, 2931, 2850, 1719, 1618, 1582, 1514, 1488, 1455, 1366, 1313, 1259, 1224, 1132, 1103, 1055, 991, 829, 735, 696 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz) δ 7.864 (s, 1 H, major), 7.857 (s, 1 H, minor), 7.61–7.57 (m, 2 H, major + minor), 7.44–7.29 (m, 8 H, major + minor), 6.452 (s, 1 H, major), 6.446 (s, 1 H, minor), 5.79 (bs, 1 H, major + minor), 5.29–5.20 (m, 4 H, major + minor), 5.04 (bs, 1 H, major + minor), 3.82 (s, 6 H, major + minor), 3.44 (s, 3 H, minor), 3.41 (s, 3 H, major), 3.39 (dd, *J* = 9.3, 6.2 Hz, 1 H, major + minor), 3.25 (s, 3 H, major), 3.16 (s, 3 H, minor), 3.24–3.19 (m, 1 H, major + minor), 2.94 (dd, *J* = 19.1, 6.4 Hz, 1 H, minor), 2.89 (dd, *J* = 19.1, 6.3 Hz, 1 H, major), 2.28 (bs, 2 H, major + minor), 1.91 (ap dt, *J* = 12.8, 6.1 Hz, 1 H, major + minor), 1.61 (ap dt, *J* = 13.4, 6.7 Hz, 1 H, major + minor), 1.10 (s, 3 H, major + minor), 0.85 (bs, 6 H, minor), 0.84 (s, 3 H, major), 0.83 (s, 3 H, major + minor) ppm; ¹³C NMR (CDCl₃, 151 MHz) δ 191.7 (major), 191.5 (minor), 184.00 (minor), 183.96 (major), 180.04 (major), 180.00 (minor), 177.5 (minor), 177.3 (major), 167.80 (major + minor), 162.93 (minor), 162.86 (major), 160.84 (major), 160.70 (minor), 159.5 (major), 159.4 (minor), 148.6 (major), 148.5 (minor), 146.7 (major), 146.6 (minor), 136.5 (major + minor), 135.0 (major + minor), 132.5 (major), 132.4 (minor), 132.2 (major + minor), 130.1 (major), 129.9 (minor), 128.7 (major + minor)*, 128.6 (major + minor)*, 128.5 (major)*, 128.3 (minor)*, 128.18 (minor)*, 128.15 (major)*, 127.9 (major + minor)*, 127.0 (major + minor)*, 125.4 (minor), 125.2 (major), 123.5 (major), 123.4 (minor), 111.62 (major), 111.57 (minor), 106.33 (minor), 106.30 (major), 102.43 (major), 102.41 (minor), 96.9 (major), 96.7 (minor), 80.6 (minor), 80.5 (major), 72.43 (minor), 72.41 (major), 71.3 (major), 71.2 (minor), 68.50 (minor), 68.46 (major), 55.57 (major), 55.55 (minor), 51.9 (major), 51.7 (minor), 49.41 (major), 49.36 (minor), 44.4 (major + minor), 37.8 (major), 37.7 (minor), 35.8 (major), 35.6 (minor), 27.0 (major + minor), 26.90 (major), 26.87 (minor), 23.1 (major + minor), 22.63 (minor), 22.56 (major), 20.0 (major), 19.9 (minor) ppm; HRMS (ESI) calcd for C₄₆H₄₃NO₁₀Na⁺ [*M*+Na]⁺ 792.2779, found 792.2787. *Due to overlapping ¹³C chemical shifts of diastereomers, these signals could not be assigned with accuracy.

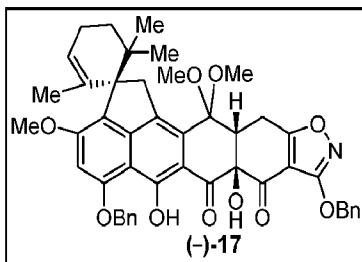


(1*R*,7*a*'*S*,12*a*'*S*)-5',9'-Bis(benzyloxy)-6',7*a*'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8'(7*a*'*H*,12'*H*)-dione (+)-16 and (1*R*,7*a*'*R*,12*a*'*R*)-5',9'-bis(benzyloxy)-6',7*a*'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8'(7*a*'*H*,12'*H*)-dione (-)-17 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): A solution of hydroxyl compound (-)-15 (450 mg, 584 μ mol, 1.0 equiv, dr ca. 4:1) in THF (32 mL) at -78°C was added dropwise a solution of NaCNBH₃ (148 mg, 2.35 mmol, 4.0 equiv) in THF (8 mL). The reaction mixture was stirred at -78°C for 1.5 h, then quenched by addition of saturated aq. NH₄Cl solution (20 mL) and allowed to warm to 25°C . The mixture was diluted with water (40 mL) and extracted with EtOAc (3 $\times$ 40 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was then purified by preparative TLC (silica gel, 10% acetone in toluene) to give naphthol (-)-17 (224 mg, 280 μ mol, 48% yield) and its distereoisomer (+)-16 (56.0 mg, 70.0 μ mol, 12% yield) as yellow powders.



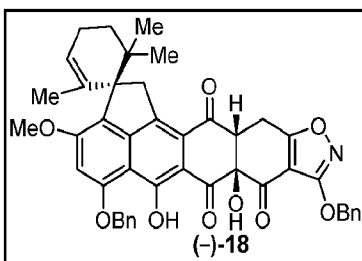
(1*R*,7*a*'*S*,12*a*'*S*)-5',9'-Bis(benzyloxy)-6',7*a*'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8'(7*a*'*H*,12'*H*)-dione (+)-16: R_f =0.50 (silica gel, acetone:toluene 1:4); $[\alpha]_D^{22} = +103$ (c =0.2, CH₂Cl₂); FT-IR (film) ν_{max} : 3400, 2940, 2921, 1717, 1593, 1514, 1485, 1448, 1408, 1370, 1345, 1306, 1235, 1219, 1130, 1104, 1048, 998, 904, 820, 735, 696 cm^{-1} ; ¹H NMR (CDCl₃, 600 MHz) δ 15.54 (s, 1 H), 7.60–7.57 (m, 2 H), 7.49–7.47 (m, 2 H), 7.42–7.30 (m, 6 H), 6.65 (s, 1 H), 5.70 (s, 1 H), 5.51 (bs, 1 H), 5.33 (s, 2 H), 5.30 (s, 2 H), 3.84 (s, 3 H), 3.82 (d, J =18.0 Hz, 1 H), 3.44 (s, 3 H), 3.35 (dd, J =10.0, 7.3 Hz, 1 H), 3.16 (dd, J =19.0, 7.5 Hz, 1 H), 3.13 (s, 3 H), 2.97 (d, J =18.3 Hz, 1 H), 2.87 (dd, J =19.0, 10.0 Hz, 1 H), 2.26–2.21 (m, 1 H), 2.08–2.02 (m, 1 H), 1.84

(ap td, $J=12.4, 6.0\text{ Hz}$, 1 H), 1.51 (s, 3 H), 1.34 (dd, $J=12.6, 5.5\text{ Hz}$, 1 H), 0.88 (s, 3 H), 0.43 (s, 3 H) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 193.4, 184.3, 179.2, 168.9, 168.0, 159.5, 159.3, 148.2, 137.2, 136.6, 135.14, 135.12, 128.8, 128.62, 128.60, 128.3, 128.0, 126.9, 123.5, 122.9, 121.3, 108.8, 107.3, 106.5, 102.5, 98.2, 78.4, 72.4, 71.6, 58.5, 55.5, 50.5, 48.0, 45.1, 43.4, 38.6, 34.1, 25.7, 24.01, 23.99, 23.0, 21.1 ppm; HRMS (ESI) calcd for $\text{C}_{46}\text{H}_{45}\text{NO}_{10}\text{Na}^+ [M+\text{Na}]^+$ 794.2936, found 794.2955.



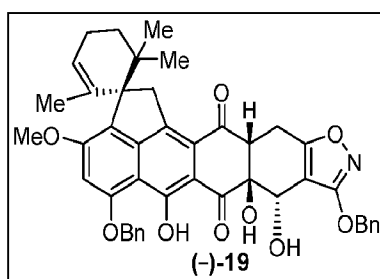
(1*R*,7*a'R*,12*a'**R*)-5',9'-Bis(benzyloxy)-6',7*a'*-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a'*,13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-**

7',8'(7*a'H*,12*H*)-dione (-)-17:** $R_f=0.60$ (silica gel, acetone:toluene 1:4); $[\alpha]_D^{22}=-70$ ($c=0.2$, CH_2Cl_2); FT-IR (film) ν_{max} : 3409, 2939, 1715, 1592, 1514, 1484, 1448, 1407, 1344, 1307, 1219, 1131, 1105, 1049, 994, 905, 735, 696 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 15.39 (s, 1 H), 7.62–7.56 (m, 2 H), 7.49–7.45 (m, 2 H), 7.42–7.39 (m, 2 H), 7.38–7.30 (m, 4 H), 6.66 (s, 1 H), 5.62 (bs, 1 H), 5.49 (bs, 1 H), 5.35–5.28 (m, 4 H), 3.84 (s, 3 H), 3.49 (d, $J=18.8\text{ Hz}$, 1 H), 3.38–3.31 (m, 1 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.16 (d, $J=18.8\text{ Hz}$, 1 H), 3.09 (dd, $J=18.8, 7.4\text{ Hz}$, 1 H), 2.84 (dd, $J=18.8, 8.4\text{ Hz}$, 1 H), 2.25–2.21 (m, 1 H), 2.09–2.02 (m, 1 H), 1.79 (ddd, $J=12.3, 12.3, 6.2\text{ Hz}$, 1 H), 1.45 (s, 3 H), 1.36 (dd, $J=12.3, 5.9\text{ Hz}$, 1 H), 0.94 (s, 3 H), 0.48 (s, 3 H) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 193.9, 184.3, 179.3, 168.4, 168.0, 159.5, 159.3, 148.3, 137.4, 136.5, 135.2, 134.5, 128.8, 128.60, 128.55, 128.2, 128.0, 126.9, 123.6, 123.2, 120.8, 109.0, 107.7, 106.3, 102.4, 98.1, 78.3, 72.4, 71.5, 58.5, 55.5, 51.2, 48.2, 45.1, 43.8, 38.1, 34.2, 25.8, 24.7, 23.5, 23.0, 21.1 ppm; HRMS (ESI) calcd for $\text{C}_{46}\text{H}_{45}\text{NO}_{10}\text{Na}^+ [M+\text{Na}]^+$ 794.2936, found 794.2954.

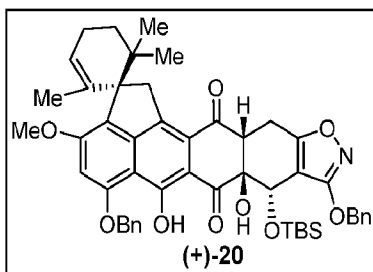


(1*R*,7*a'R*,12*a'**R*)-5',9'-Bis(benzyloxy)-6',7*a'*-dihydroxy-3'-methoxy-2,6,6-trimethyl-12',12*a'*-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8',13'(7*a'**H*)-trione (-)-18** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a solution of ketal (-)-17 (155 mg, 201 μmol , 1.0 equiv) in THF (15 mL) was added 2 N aq. HCl (1.6 mL). The reaction mixture was stirred at 25 $^\circ\text{C}$ for 5 h and was then diluted with water (30 mL) and extracted with EtOAc (50 mL). The organic phase was washed with water (50 mL) and brine (50 mL), and then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give analytically pure triketone (-)-18 (145 mg, 201 μmol , quant. yield) as a yellow foam. (-)-18:

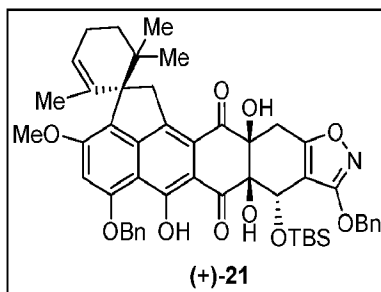
$R_f=0.70$ (silica gel, EtOAc:hexanes 2:3); $[\alpha]_D^{22} = -27$ ($c=0.1$, CH_2Cl_2); FT-IR (film) ν_{max} : 3448, 2962, 2918, 1696, 1609, 1585, 1513, 1481, 1446, 1402, 1344, 1327, 1292, 1258, 1199, 1158, 1132, 1108, 1037, 908, 825, 731, 696 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 13.91 (s, 1 H), 7.62–7.59 (m, 2 H), 7.46–7.42 (m, 2 H), 7.41–7.39 (m, 2 H), 7.36 (m, 1 H), 7.34–7.28 (m, 3 H), 6.77 (s, 1 H), 5.49 (bs, 1 H), 5.33 (s, 2 H), 5.29 (d, $J=12.0$ Hz, 1 H, AB system), 5.26 (d, $J=12.0$ Hz, 1 H, AB system), 4.94 (s, 1 H), 3.89–3.82 (m, 5 H), 3.66 (d, $J=20.0$ Hz, 1 H), 3.33 (dd, $J=17.3, 4.8$ Hz, 1 H), 3.15 (d, $J=20.0$ Hz, 1 H), 2.19 (m, 1 H), 2.03 (m, 1 H), 1.80 (ddd, $J=12.7, 12.7, 6.2$ Hz, 1 H), 1.45 (s, 3 H), 1.30 (dd, $J=12.7, 5.6$ Hz, 1 H), 0.88 (s, 3 H), 0.30 (s, 3 H) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 195.5, 192.0, 184.8, 181.7, 168.1, 164.6, 159.4, 159.1, 147.7, 142.3, 136.2, 136.1, 135.0, 128.8, 128.6, 128.5, 128.24, 128.21, 127.2, 127.0, 121.8, 121.4, 110.2, 107.8, 105.3, 100.2, 78.5, 72.4, 71.7, 59.6, 55.6, 53.0, 45.5, 38.4, 34.0, 25.4, 24.2, 22.9, 20.9, 20.7 ppm; HRMS (ESI) calcd for $\text{C}_{44}\text{H}_{39}\text{NO}_9\text{Na}^+$ $[M+\text{Na}]^+$ 748.2517, found 748.2531.



(1*R*,7*a*'*S*,8'*S*,12*a*'*R*)-5',9'-bis(benzyloxy)-6',7*a*',8'-trihydroxy-3'-methoxy-2,6,6-trimethyl-7*a*',8',12',12*a*'-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (-)-19 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a solution of triketone (-)-18 (98.0 mg, 135 μmol , 1.0 equiv) in anhydrous EtOAc:acetone (1:1, 10 mL) at 25 $^\circ\text{C}$ was added sodium triacetoxyborohydride (34.1 mg, 162 μmol , 1.2 equiv) and the solution was warmed to 40 $^\circ\text{C}$ for 2 h. The reaction mixture was then allowed to cool to 25 $^\circ\text{C}$, diluted with water (20 mL) and extracted with EtOAc (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 10% acetone in toluene) to give diol (-)-19 (45.2 mg, 62.1 μmol , 46%) as a yellow foam. (-)-19: $R_f=0.50$ (silica gel, EtOAc:hexanes 3:7); $[\alpha]_D^{22} = -5$ ($c=0.1$, CH_2Cl_2); FT-IR (film) ν_{max} : 3475, 2961, 2920, 2855, 1693, 1662, 1586, 1512, 1483, 1446, 1403, 1341, 1293, 1260, 1199, 1162, 1132, 1113, 1036, 908, 732, 696 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 14.41 (s, 1 H), 7.62–7.60 (m, 2 H), 7.46–7.43 (m, 2 H), 7.40–7.31 (m, 6 H), 6.73 (s, 1 H), 5.49 (bs, 1 H), 5.36 (d, $J=12.1$ Hz, 1 H, AB system), 5.33 (d, $J=12.1$ Hz, 1 H, AB system), 5.27 (d, $J=11.7$ Hz, 1 H, AB system), 5.23 (d, $J=11.7$ Hz, 1 H, AB system), 4.59 (d, $J=3.9$ Hz, 1 H), 4.17 (s, 1 H), 3.85 (s, 3 H), 3.82 (d, $J=17.6$ Hz, 1 H), 3.67 (d, $J=6.9$ Hz, 1 H), 3.54 (d, $J=19.5$ Hz, 1 H), 3.24 (d, $J=19.5$ Hz, 1 H), 2.92 (dd, $J=17.6, 6.9$ Hz, 1 H), 2.19 (m, 1 H), 2.03 (m, 1 H), 1.82 (ddd, $J=12.7, 12.7, 6.0$ Hz, 1 H), 1.68 (d, $J=3.9$ Hz, 1 H), 1.46 (s, 3 H), 1.29 (dd, $J=12.7, 6.0$ Hz, 1 H), 0.87 (s, 3 H), 0.31 (s, 3 H) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 201.1, 193.0, 169.6, 169.3, 164.8, 159.4, 159.3, 148.0, 138.8, 136.5, 136.4, 135.7, 128.9, 128.72, 128.68, 128.5, 128.2, 127.1, 126.5, 124.2, 121.5, 110.0, 109.9, 103.8, 99.5, 77.1, 71.8, 71.7, 68.5, 59.6, 55.6, 50.5, 44.9, 38.5, 34.0, 25.5, 24.2, 23.0, 21.0, 18.7 ppm; HRMS (ESI) calcd for $\text{C}_{44}\text{H}_{41}\text{NO}_9\text{Na}^+$ $[M+\text{Na}]^+$ 750.2674, found 750.2696.

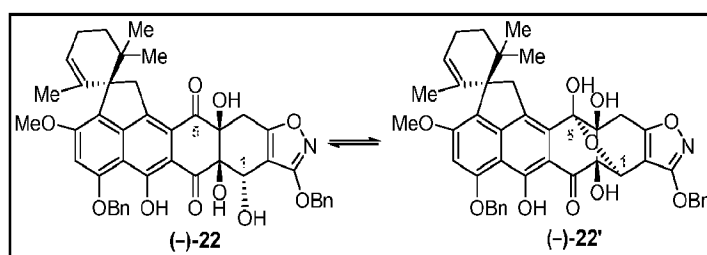


(1*R*,7*a*'*S*,8'*R*,12*a*'*R*)-5',9'-Bis(benzyloxy)-8'-[[*tert*-butyl(dimethyl)silyl]oxy]-6',7*a*'-dihydroxy-3'-methoxy-2,6,6-trimethyl-7*a*',8',12',12*a*'-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (+)-20 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a stirred solution of diol (–)-19 (28.0 mg, 38.0 μmol, 1.0 equiv) in CH₂Cl₂ (2.8 mL) was added freshly distilled 2,6-lutidine (70.0 μL, 570 μmol, 15 equiv). The reaction mixture was cooled to 0 °C, and freshly distilled TBSOTf (85.0 μL, 380 μmol, 10 equiv) was added. The reaction mixture was allowed to warm to 25 °C and stirred for 15 minutes. Three additional portions of 2,6-lutidine (70 μL, each) and TBSOTf (85 μL, each) were added to the reaction flask in 15 minute intervals (0 °C to 25 °C) and the mixture was stirred for an additional 1 h at 25 °C. The reaction was then quenched by addition of saturated aq. NaHCO₃ solution (5 mL) (vigorous bubbling) and extracted with CH₂Cl₂ (2×5 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Residual volatiles were then azeotropically removed with toluene (twice). The crude material was then purified by preparative TLC (silica gel, 5% acetone in toluene) to give the TBS-ether (+)-20 (24.2 mg, 28.9 mmol, 76%) as a yellow foam. (+)-20: R_f=0.40 (silica gel, 5% acetone in toluene); [α]_D²² = +68 (*c*=0.1, CH₂Cl₂); FT-IR (film) ν_{max}: 3479, 2927, 2856, 1697, 1656, 1605, 1589, 1510, 1473, 1448, 1405, 1343, 1295, 1260, 1205, 1166, 1135, 1082, 1048, 838, 779, 736, 697 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz) δ 14.53 (s, 1H), 7.61–7.57 (m, 2H), 7.44–7.39 (m, 4H), 7.37–7.31 (m, 4H), 6.72 (s, 1H), 5.49 (bs, 1H), 5.35 (d, *J*=12.1 Hz, 1H, AB system), 5.32 (d, *J*=12.1 Hz, 1H, AB system), 5.28 (d, *J*=11.5 Hz, 1H, AB system), 5.21 (d, *J*=11.5 Hz, 1H, AB system), 4.56 (s, 1H), 4.02 (bs, 1H), 3.91 (d, *J*=17.9 Hz, 1H), 3.84 (s, 3H), 3.59 (d, *J*=7.4 Hz, 1H), 3.56 (d, *J*=19.9 Hz, 1H), 3.22 (d, *J*=19.9 Hz, 1H), 2.86 (dd, *J*=17.9, 7.4 Hz, 1H), 2.19 (m, 1H), 2.03 (m, 1H), 1.84 (m, 1H), 1.44 (s, 3H), 1.27 (m, 1H), 0.89 (s, 3H), 0.33 (s, 3H), 0.31 (s, 9H), –0.26 (s, 3H), –0.53 (s, 3H) ppm; ¹³C NMR (CDCl₃, 151 MHz) δ 202.2, 191.8, 169.5, 169.4, 165.1, 159.3, 159.2, 147.9, 138.5, 136.6, 136.4, 135.5, 129.0, 128.8, 128.7, 128.6, 128.1, 127.1, 126.4, 124.5, 121.4, 110.4, 109.7, 104.5, 99.8, 77.8, 71.9, 71.8, 69.2, 59.6, 55.5, 50.2, 45.1, 38.5, 34.0, 25.5, 25.2, 24.2, 23.0, 20.9, 18.4, 17.7, –5.47, –5.50 ppm; HRMS (ESI) calcd for C₅₀H₅₅NO₉SiNa⁺ [*M*+Na]⁺ 864.3538, found 864.3553.



(1*R*,7*a**R*,8*R*,12*a**S*)-5',9'-Bis(benzyloxy)-8'-[*tert*-butyl(dimethyl)silyl]oxy]-6',7*a*',12*a*'-trihydroxy-3'-methoxy-2,6,6-trimethyl-7*a*',8',12',12*a*'-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (+)-**21** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): A solution of TBS-ether (+)-**20** (22 mg, 0.026 mmol, 1.0 equiv) in THF (0.4 mL) was cooled to -78°C , and KHMDS solution (1 M in THF, 88 μL , 88 μmol , 3.4 equiv) was added dropwise. After stirring for 1 h at -78°C , freshly prepared recrystallized Davis oxaziridine (Vishwakarma *et al.*, 1988) (26 mg, 100 μmol , 3.9 equiv) in THF (0.15 mL) was added, and the mixture was stirred for 2 h at -78°C . Then, the reaction was quenched by addition of MeOH (0.2 mL), followed by dimethyl sulfide (0.1 mL) and saturated aq. NH_4Cl solution (2.0 mL). The mixture was extracted with CH_2Cl_2 ($3 \times 10\text{ mL}$), and the combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 5% acetone in toluene), gave product (+)-**21** (7.2 mg, 8.3 μmol , 32% yield, 55% yield brsm) as an orange foam and recovered contaminated starting material (+)-**20**, which was purified by a second preparative TLC with 1.25% acetone in CH_2Cl_2 [(+)-**20**, 9.2 mg, 11 μmol , 42% yield]. (+)-**21**: $R_f=0.40$ (silica gel, acetone:toluene 1:9); $[\alpha]_D^{22}=+27$ ($c=0.1$, CH_2Cl_2); FT-IR (film) ν_{max} : 3460, 2921, 2856, 1702, 1606, 1588, 1509, 1473, 1447, 1403, 1340, 1320, 1267, 1205, 1136, 1050, 910, 838, 780, 734, 696 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 14.09 (s, 1 H), 7.59–7.57 (m, 2 H), 7.45–7.39 (m, 4 H), 7.38–7.33 (m, 4 H), 6.72 (s, 1 H), 5.50 (bs, 1 H), 5.36 (d, $J=12.4\text{ Hz}$, 1 H, AB system), 5.33 (d, $J=12.4\text{ Hz}$, 1 H, AB system), 5.28 (d, $J=11.4\text{ Hz}$, 1 H, AB system), 5.20 (d, $J=11.4\text{ Hz}$, 1 H, AB system), 4.62 (s, 1 H), 4.29 (s, 1 H), 4.15 (d, $J=17.6\text{ Hz}$, 1 H), 3.84 (s, 3 H), 3.55 (d, $J=19.4\text{ Hz}$, 1 H), 3.22 (d, $J=19.4\text{ Hz}$, 1 H), 3.00 (s, 1 H), 2.68 (d, $J=17.6\text{ Hz}$, 1 H), 2.19 (m, 1 H), 2.03 (m, 1 H), 1.84 (m, 1 H), 1.46 (s, 3 H), 1.28 (m, 1 H), 0.88 (s, 3 H), 0.35 (s, 3 H), 0.32 (s, 9 H), -0.26 (s, 3 H), -0.54 (s, 3 H) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 200.8, 190.2, 169.7, 169.1, 164.2, 159.2, 159.1, 147.8, 140.4, 136.6, 136.4, 135.4, 129.1, 128.81, 128.76, 128.6, 128.1, 127.1, 126.5, 123.2, 121.4, 110.6, 109.8, 104.3, 100.1, 80.8, 77.5, 72.0, 71.8, 68.5, 59.7, 55.5, 44.9, 38.6, 34.0, 28.7, 25.4, 25.2, 24.2, 23.0, 20.9, 17.7, -5.4 , -5.6 ppm; HRMS (ESI) calcd for $\text{C}_{50}\text{H}_{55}\text{NO}_{10}\text{SiNa}^+ [M+\text{Na}]^+$ 880.3487, found 880.3528.

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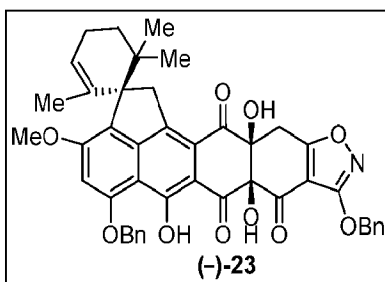


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(1*R*,7*a**R*,8*S*,12*a**S*)-5',9'-Bis(benzyloxy)-6',7*a*',8',12*a*'-tetrahydroxy-3'-methoxy-2,6,6-trimethyl-7*a*',8',12',12*a*'-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (–)-**22**/ (1*R*,7*a**R*,8*S*,12*a**S*,13*S*)-5',9'-bis(benzyloxy)-6',7*a*',12*a*',13'-tetrahydroxy-3'-methoxy-2,6,6-trimethyl-1',7*a*',8',12',12*a*',13'-hexahydro-7'*H*-spiro[cyclohex-2-ene-1,2'-[11,14]dioxal[10]aza[8,13]epoxycyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazol]-7'-one (–)-**22'** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Diol (+)-**21** (8.3 mg, 9.7 μmol , 1.0 equiv) was dissolved in MeCN (0.3 mL) in a plastic vial and cooled to 0°C . HF•pyridine (70% HF in pyridine, 16 μL) was added, and the mixture was warmed to 55°C . After 2 h, 8 h, and 14 h, an additional portion of HF•pyridine (70% HF in pyridine, 40 μL

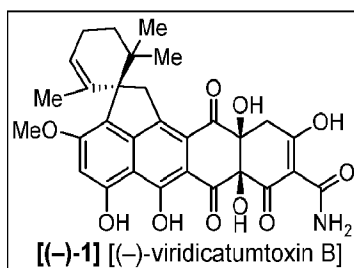
each; 0 to 55 °C) was added. After 20 h the reaction mixture was allowed to cool to 25 °C, diluted with EtOAc (4 mL), and carefully quenched by addition of saturated aq. NaHCO₃ solution (4 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2×15 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 20% acetone in toluene) afforded triol (–)-**22**/(–)-**22'** (5.2 mg, 7.0 μmol, 72% yield) as a yellow foam. *(–)-**22**/(–)-**22'**: R_f=0.40 (silica gel, acetone:toluene 1:9); [α]_D²² = –42 (c=0.1, CH₂Cl₂); FT-IR (film) ν_{max}: 3460, 2923, 1698, 1590, 1513, 1483, 1448, 1403, 1341, 1323, 1264, 1205, 1134, 1044, 816, 738, 697 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz, 298 K) δ 14.02 (bs, 1 H), 7.61–7.58 (m, 2 H), 7.46–7.28 (m, 8 H), 6.73 (s, 1 H), 5.50 (bs, 1 H), 5.34 (d, *J* = 12.1 Hz, 1 H, AB system), 5.31 (d, *J* = 12.1 Hz, 1 H, AB system), 5.35–5.12 (m, 2 H), 5.10–2.80 (m, 5 H), 3.85 (s, 3 H), 2.76 (d, *J* = 17.3 Hz, 1 H), 2.19 (m, 1 H), 2.03 (m, 1 H), 1.83 (m, 1 H), 1.47 (s, 3 H), 1.29 (m, 1 H), 0.88 (s, 3 H), 0.37 (bs, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃, 298 K) δ 199.7, 171.2, 169.2, 159.4 (b), 159.2, 147.7, 136.4, 136.1, 135.6, 128.7, 128.6, 128.5, 128.3, 127.1, 126.9, 121.6, 110.0, 99.8, 71.7, 71.6, 59.7, 55.5, 44.5, 38.5, 33.9, 33.5, 31.9, 29.6, 29.5, 29.4, 29.2, 29.1, 25.4, 24.7, 24.1, 22.8, 22.7, 21.1 ppm; HRMS (ESI) calcd for C₄₄H₄₁NO₁₀Na⁺ [*M*+Na]⁺ 766.2623, found 766.2640.

*Without wishing to be bound by any theory, it is believed that the hydroxy ketone **22** exists in equilibrium with its cyclic hemiacetal isomer **22'**. At T=298 K, slow interconversion between these two species is observed in CDCl₃, which results in broad signals in the ¹H and ¹³C NMR spectra. Due to signal broadening, not all the ¹H and ¹³C signals could be identified with accuracy (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014).



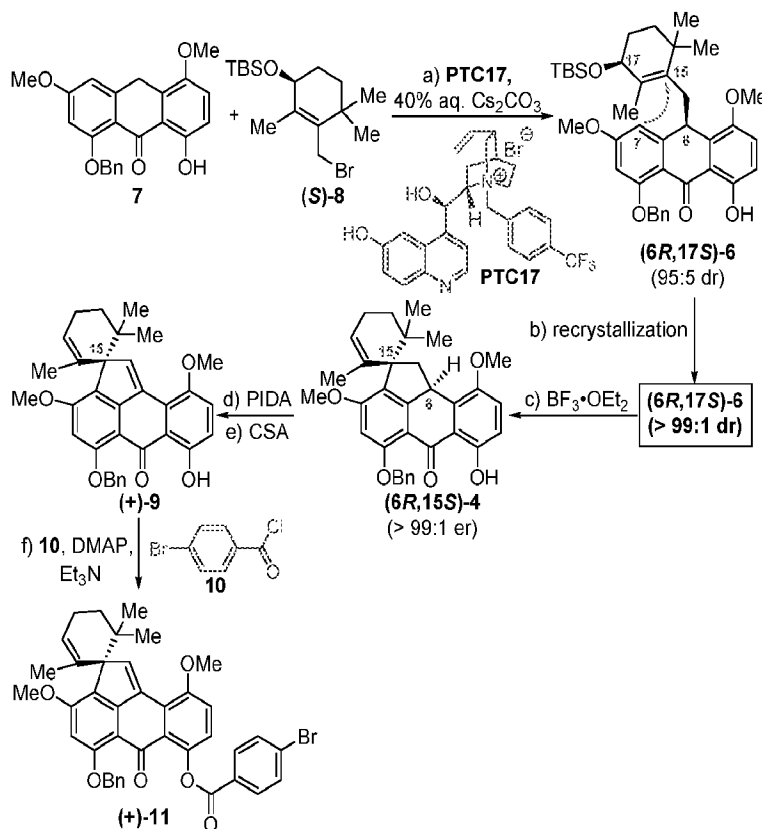
(1*R*,7*a'**R*,12*a'**S*)-5',9'-Bis(benzyloxy)-6',7*a'*,12*a'*-trihydroxy-3'-methoxy-2,6,6-trimethyl-12',12*a'*-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8',13'(7*a'**H*)-trione (–)-**23** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): A solution of triol (–)-**22**/(–)-**22'** (5.0 mg, 6.7 μmol, 1.0 equiv) in (CH₂)₂Cl₂ (DCE, 360 μL) was cooled to 0 °C, and Dess–Martin periodinane⁴⁰ (0.3 M solution in CH₂Cl₂, 27 μL, 3.4 mg, 8.1 μmol, 1.2 equiv) was added. After stirring for 30 minutes at 0 °C, the mixture was allowed to warm up to 25 °C and stirred for 1.5 h. Then, the reaction mixture was warmed up to 50 °C, and one additional portion of Dess–Martin periodinane (0.3 M solution in CH₂Cl₂, 14 μL, 1.7 mg, 4.1 μmol, 0.6 equiv, 0 to 50 °C) was added after 1 h. After 2 h at 50 °C, TLC analysis indicated complete conversion. The reaction mixture was allowed to cool to 25 °C, and then quenched by addition of saturated aq. NaHCO₃:saturated aq. Na₂S₂O₃ solution (1:1, 5 mL). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2×5 mL). The combined organic phases were washed with brine (5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 5% acetone in CH₂Cl₂) afforded triketone (–)-**23** (4.1 mg, 5.5 μmol, 82% yield) as a yellow powder. (–)-**23**: R_f=0.50 (silica gel,

acetone:toluene 1:9); $[\alpha]_D^{22} = -107$ ($c=0.1$, CH_2Cl_2), FT-IR (film) ν_{max} : 3451, 2919, 1715, 1613, 1586, 1516, 1485, 1447, 1403, 1342, 1274, 1203, 1186, 1140, 1091, 1027, 965, 737, 696 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 600 MHz) δ 14.11 (s, 1H), 7.61–7.58 (m, 2H), 7.54–7.42 (m, 2H), 7.47–7.39 (m, 5H), 7.36 (m, 1H), 6.85 (s, 1H), 5.54 (bs, 1H), 5.37 (s, 2H), 5.35–5.30 (m, 2H), 4.63 (s, 1H), 4.29 (s, 1H), 4.05 (d, $J=18.9$ Hz, 1H), 3.90 (s, 3H), 3.42 (d, $J=18.4$ Hz, 1H), 3.16 (d, $J=18.4$ Hz, 1H), 3.06 (d, $J=19.8$ Hz, 1H), 2.24 (m, 1H), 2.09 (m, 1H), 1.89 (ap td, $J=11.8, 5.7$ Hz, 1H), 1.49 (s, 3H), 1.40 (dd, $J=12.9, 5.7$ Hz, 1H), 0.94 (s, 3H), 0.46 (s, 3H) ppm; ^{13}C NMR (CD_2Cl_2 , 151 MHz) δ 194.9, 194.7, 185.1, 179.1, 167.9, 166.8, 160.5, 159.9, 147.9, 143.7, 136.7, 136.4, 135.5, 129.2, 129.06, 129.05, 128.97, 128.5, 127.54, 127.47, 122.1, 118.2, 110.4, 108.6, 106.4, 100.7, 83.9, 81.0, 73.1, 72.0, 60.3, 56.0, 44.5, 38.7, 34.8, 34.4, 25.6, 24.4, 23.3, 20.9 ppm; HRMS (ESI) calcd for $\text{C}_{44}\text{H}_{39}\text{NO}_{10}\text{Na}^+ [M+\text{Na}]^+$ 764.2466, found 764.2489.

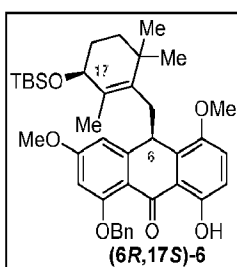


(1*R*,7*a*'*R*,11*a*'*S*)-5',6',7*a*',10',11*a*'-Pentahydroxy-3'-methoxy-2,6,6-trimethyl-7',8',12'-trioxo-7',7*a*',8',11',11*a*',12'-hexahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[*de*]tetracene]-9'-carboxamide [Synthetic (-)-viridicatumtoxin B, (-)-1] (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Triketone (-)-23 (4.0 mg, 5.4 μmol , 1.0 equiv) was dissolved in anhydrous 1,4-dioxane:MeOH (1:1, 1.0 mL) under argon and Pd black (2.8 mg, 26.5 μmol , 4.9 equiv) was added. The suspension was degassed, placed under a hydrogen atmosphere, and stirred for 10 minutes at 25 $^{\circ}\text{C}$, after which time the hydrogen balloon was removed, the flask was flushed with argon and the suspension was filtered (Celite[®]; MeOH: CH_2Cl_2 1:9). The resulting solution was concentrated under reduced pressure to give crude product [(-)-1] (4.2 mg). This product was purified by reverse-phase preparative HPLC (Shimazu HPLC, Atlantis prep T3 OBD column, 16 $\times$ 150 mm, 5 μm particle size, 5 mL/min, 85% MeCN in H_2O + 0.07% TFA buffer, $\lambda=220$ nm: $t=10.643$ min) to provide pure (-)-viridicatumtoxin B [(-)-1, 2.9 mg, 5.1 μmol , 96%] as a yellow powder. (-)-1: $R_f=0.10$ (silica gel, MeOH: CH_2Cl_2 1:9); $[\alpha]_D^{22} = -116$ ($c=0.1$, EtOH), FT-IR (film) ν_{max} : 3423, 2921, 2855, 1623, 1587, 1491, 1449, 1400, 1260, 1190, 1142, 1089, 798 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 17.89 (s, 1H), 14.72 (s, 1H), 9.20 (s, 1H), 8.74 (s, 1H), 6.80 (s, 1H), 6.02 (bs, 1H), 5.53 (bs, 1H), 4.03 (d, $J=19.8$ Hz, 1H), 3.90 (s, 3H), 3.11 (d, $J=18.8$ Hz, 1H), 3.04 (d, $J=19.8$ Hz, 1H), 2.81 (d, $J=18.8$ Hz, 1H), 2.22 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.46 (s, 3H), 1.40 (m, 1H), 0.93 (s, 3H), 0.46 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 151 MHz) δ 195.2, 194.3, 192.8, 188.8, 173.0, 165.4, 161.3, 158.4, 146.4, 144.8, 135.8, 127.3, 122.0, 117.1, 107.3, 106.9, 102.6, 99.7, 80.7, 77.7, 60.6, 55.8, 44.6, 42.1, 38.5, 34.2, 25.6, 24.5, 23.0, 20.9 ppm; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{29}\text{NO}_{10}\text{Na}^+ [M+\text{Na}]^+$ 586.1584, found 586.1681.

Enantioselective Total Synthesis and Absolute Configuration of (+)-Viridicatumtoxin B

Scheme 16. Enantioselective Synthesis of the *BCDEF* Fragment (*6R,15S*)-4 of (+)-Viridicatumtoxin B and Its Absolute Configuration

- 5 Note: to avoid confusion, the numbering on **(6R,17S)-6**, **(6R,15S)-4** and **(+)-9** in this Scheme is based on the viridicatumtoxin numbering, as opposed to the carbon numbering of compound **(10R,14S)-6**, which is the same compound **(6S,17R)-6**, but numbered based on the anthrone numbering.

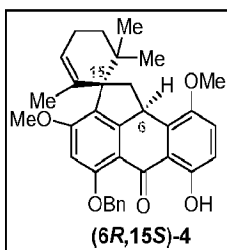


- 10 **(10R)-1-(Benzyloxy)-10-[[[(3R)-3-[[*tert*-butyl(dimethyl)silyl]oxy]-2,6,6-trimethylcyclohex-1-en-1-yl]methyl]-8-hydroxy-3,5-dimethoxyanthracen-9(10H)-one [(6R,17S)-6]:** To a stirred mixture of anthrone **7** (6.02 g, 16.0 mmol, 1.0 equiv), allylic bromide **(S)-8** (6.12 g, 17.6 mmol, 1.1 equiv) and **PTC17** (44.0 mg, 80.0 μmol , 0.005 equiv) in $(\text{CH}_2)_2\text{Cl}_2$ (160 mL) under argon, was added 50% aq. KOH (48 mL) dropwise at -30°C . The reaction mixture was stirred vigorously at -30°C for 240 h (10 days). The mixture was then
- 15 quenched by addition of water (300 mL) and extracted with CH_2Cl_2 ($3 \times 300\text{ mL}$). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (10% EtOAc:hexanes) gave chiral alkylated anthrone **(6R,17S)-**

6 (6.49 g, 11.7 mmol, 73% yield, 95:5 dr) as a yellow foam. Compound **(6*R*,17*S*)-6** is the same as **(10*R*,14*S*)-6**, the latter is numbered based on the anthrone numbering. The diastereomeric ratio of the product **(6*R*,17*S*)-6** was determined by HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 98/2, 220 nm): 5.36 min for **(6*R*,17*S*)-6**; 9.66 min for **(6*S*,17*S*)-6**. (see below).

5

This material was enriched by crystallization from hexanes [precipitating crystals were racemic **(17*S*)-6** while the mother liquor contained the enriched **(6*R*,17*S*)-6** (5.91 g, 10.6 mmol, 91% yield, > 99:1 dr) (see below). **(6*R*,17*S*)-6**: $[\alpha]_D^{22} = -95.1$ ($c = 1.0$, CH₂Cl₂ 95:5 dr). The other physical and spectroscopic data of this compound matched those mentioned above for **(10*R*,14*S*)-6**.

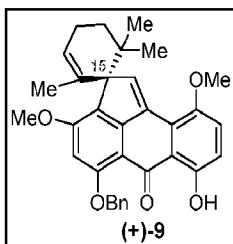


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(2*S*,10*bR*)-5-(Benzyloxy)-7-hydroxy-3,10-dimethoxy-2',6',6'-trimethyl-1,10*b*-dihydro-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]en]-6-one [(6*R*,15*S*)-4**]: Chiral alkylated anthrone **(6*R*,17*S*)-6** (5.00 g, 7.78 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (500 mL) and cooled to -78 °C. A freshly prepared solution of BF₃•OEt₂ (3.9 mL of a 0.1 M in CH₂Cl₂, 390 μmol, 0.05 equiv) was added dropwise, and the reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 0.5 h. The reaction was quenched by addition of saturated aq. NaHCO₃ solution (300 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (300 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5%→10% EtOAc:hexanes) to give chiral *BCDEF* spirocycle **(6*R*,15*S*)-4** (3.02 g, 5.91 mmol, 76% yield, 99.2:0.8 er) as a yellow foam. The enantiomeric ratio was determined by HPLC (Chiralcel OD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 7.29 min for **(6*R*,15*S*)-4**; 9.79 min for **(6*S*,15*R*)-4**. (see below). **(6*R*,15*S*)-4**: $[\alpha]_D^{22} = -64.8$ ($c = 1.0$, CH₂Cl₂, 99.2:0.8 er). The other physical and spectroscopic data of this compound were identical to those mentioned above for compound **(6*S*,15*R*)-4**.**

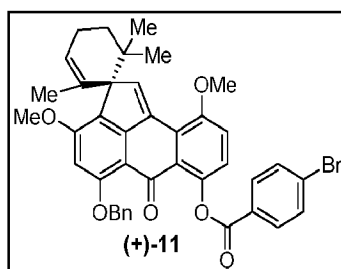
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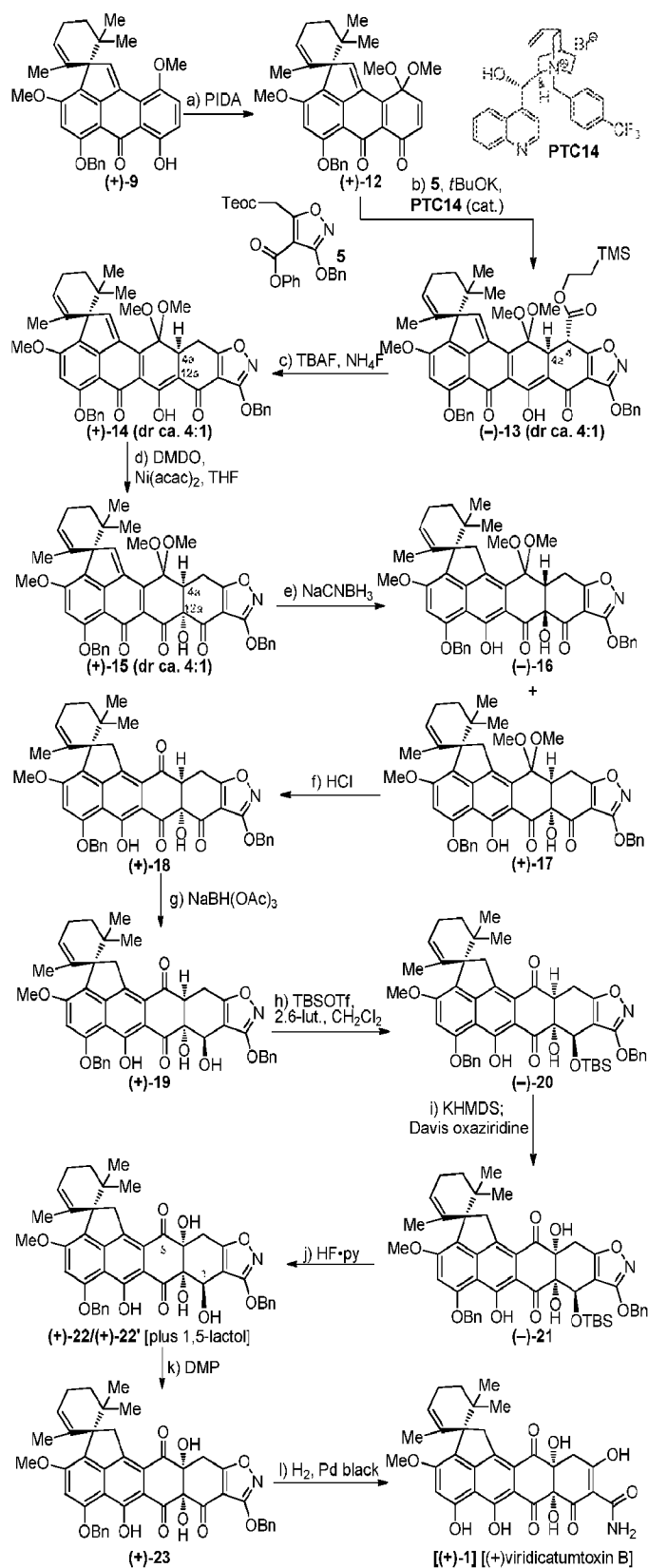
(2*S*)-5-(Benzyloxy)-7-hydroxy-3,10-dimethoxy-2',6',6'-trimethyl-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]en]-6-one (+)-**9**: Spirocycle (**6*R*,15*S***)-**4** (3.00 g, 5.88 mmol, 1.0 equiv) was dissolved in MeOH:CH₂Cl₂ (1:1, 120 mL), and the solution was cooled to 0 °C. Freshly prepared PhI(OAc)₂³⁷ (2.27 g, 7.05 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 30 minutes at 0 °C and for 30 additional minutes at 25 °C. The reaction was quenched by addition of saturated aq. NaHCO₃ (300 mL) and extracted with EtOAc (2×300 mL). The combined organic phases were washed with brine (150 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The so-obtained crude ketal was dissolved in CH₂Cl₂ (120 mL), and freshly crystallized CSA (95.0 mg, 0.410 mmol, 0.07 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C for 5 minutes and was then quenched by addition of saturated aq. NaHCO₃ solution (100 mL). The layers were separated, and the organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give crude product (+)-**9**. Flash column chromatography (silica gel, 2% EtOAc:toluene) gave pure intermediate (+)-**9** (2.39 g, 4.70 mmol, 80% yield for two steps) as a red solid. Compound (+)-**9** is the enantiomer of compound (–)-**9**. The enantiomeric ratio was determined by HPLC (Chiralcel OD-H, 25 °C, flow rate: 1 mL/min, hexanes/*i*PrOH: 90/10, 220 nm): 9.07 min for (–)-**9** [(**15*S***)-**9**], 9.65 min for (**15*R***)-**24**., 9.14 min for (+)-**9** [(**15*R***)-**9**]. (+)-**9**: [α]_D²² = +132 (*c*=0.05, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**9**.

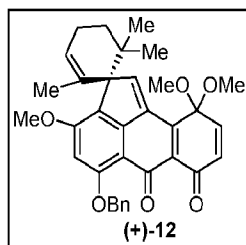


(2*S*)-5-(Benzyloxy)-3,10-dimethoxy-2',6',6'-trimethyl-6-oxo-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]en]-7-yl 4-bromobenzoate (+)-**11**: To a solution of quinomethide (+)-**9** (20 mg, 39 μmol, 1.0 equiv) in CH₂Cl₂ (3 mL) was added 4-bromobenzoyl chloride **10** (44 mg, 0.20 mmol, 5 equiv), 4-dimethylaminopyridine (DMAP, 48 mg, 0.39 mmol, 10 equiv) and triethylamine (Et₃N, 170 μL, 120 mg, 1.2 mmol, 30 equiv). The reaction mixture was stirred at 25 °C for 6 h before it was quenched by addition of saturated aq. NaHCO₃ solution (6 mL) and extracted with CH₂Cl₂ (2×6 mL). The combined organic phases were dried over Na₂SO₄, and concentrated under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc:hexanes) gave protected *p*-bromobenzoate (+)-**11** (26 mg, 37 μmol, 95% yield) as a yellow solid. Crystalization from CH₂Cl₂/hexanes 1:4 gave crystals suitable for X-ray crystallographic analysis, which revealed its absolute configuration as shown below (FIG. 6).

(+)-**11**: [α]_D²² = +88 (*c*=0.1, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**11**.

Scheme 17. Total Synthesis of Enantiopure (+)-Viridicatumtoxin B [(+)-1]

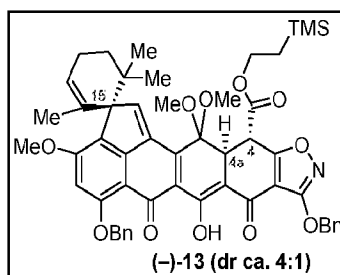




(2*S*)-5-(Benzyloxy)-3,10,10-trimethoxy-2',6',6'-trimethyl-6*H*-spiro[aceanthrylene-2,1'-cyclohex[2]ene]-6,7(10*H*)-dione (+)-12 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Quinomethide (+)-9 (2.10 g, 4.13 mmol, 1.0 equiv) was dissolved in a mixture of CH₂Cl₂:MeOH (1:10; 88 mL), and freshly prepared

5 PhI(OAc)₂³⁷ (1.60 g, 4.96 mmol, 1.2 equiv) was added. The reaction mixture was stirred at 25 °C for 1.5 h and was then quenched by addition of saturated aq. NaHCO₃ solution (80 mL). The mixture was diluted with water and extracted with CH₂Cl₂ (160 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 10% acetone in toluene, 0.1% Et₃N) to

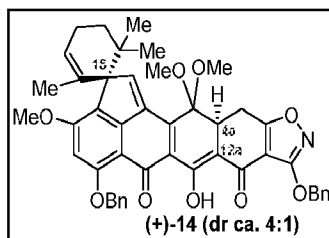
10 give diketone ketal (+)-12 (1.99 g, 3.68 mmol, 89% yield) as a yellow solid. (+)-12: [α]_D²² = +138 (*c* = 0.1, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-12.



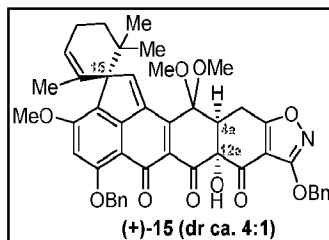
2-(Trimethylsilyl)ethyl (1*S*,12'*S*,12*a*'*S*)-5',9'-bis(benzyloxy)-7'-hydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-6',8'-dioxo-8',12',12*a*',13'-tetrahydro-6'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-12'-carboxylate (–)-13 (ca. 4:1 mixture of C15–C4/C4a diastereomers): To a solution of pentacycle (+)-12 (1.50 g, 2.76 mmol, 1.0 equiv), potassium *tert*-butoxide (372 mg, 3.31 mmol, 1.2 equiv) and PTC-14 (14.7 mg, 27.6 μmol, 0.01 equiv) in toluene (28 mL) under argon was added dropwise a solution of phenyl ester isoxazole **5**³⁰ (1.38 g, 3.04 mmol, 1.1 equiv) in toluene (28 mL) at –78 °C, and the resulting solution was then warmed to –50 °C and stirred at this temperature for 48 h. Then, the

15 reaction was quenched by addition of saturated aq. NH₄Cl solution (60 mL). The phases were separated, and the organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 2%→5% acetone in toluene) to give product (–)-13 (2.18 g, 2.40 mmol, 87% yield, dr ca. 4:1) as a yellow foam. (–)-13: [α]_D²² = –157 (*c* = 0.1, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (+)-13.

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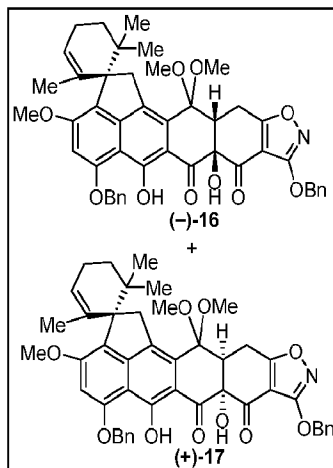


(1*S*,12*a*'*S*)-5',9'-Bis(benzyloxy)-7'-hydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-6'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-6',8'(12'*H*)-dione (+)-**14** (ca. 4:1 mixture of C15–C4*a* diastereomers) [Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014]: A solution of Teoc-heptacycle (–)-**13** (2.00 g, 2.23 mmol, 1.0 equiv, d.r. ca. 4:1) and NH₄F (1.69 g, 44.6 mmol, 20 equiv) in THF (250 mL) was degassed three times with argon at –78 °C, and the reaction flask was shielded from light using aluminum foil. A freshly prepared solution of tetra-*n*-butylammonium fluoride (22.3 mL, 1 M solution in THF, 22.3 mmol, 10 equiv, prepared from TBAF·3H₂O) was added in one portion at –78 °C. The reaction mixture was warmed to 25 °C and stirred for 10 minutes. The reaction was then quenched by addition of brine (150 mL) and extracted with EtOAc (150 mL). The layers were separated, and the organic phase was washed with water (3 × 120 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 2%→5% acetone in toluene) to give heptacycle (+)-**14** (1.42 g, 1.90 mmol, 85% yield, dr ca. 4:1) as an orange foam. (+)-**14**: [α]_D²² = +26 (*c* = 0.05, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**14**.

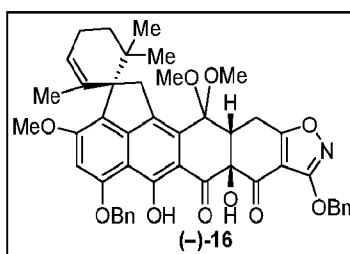


(1*S*,7*a*'*R*,12*a*'*S*)-5',9'-Bis(benzyloxy)-7*a*'-hydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-6'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-6',7',8'(7*a*'*H*,12'*H*)-trione (+)-**15** (ca. 4:1 mixture of C15–C4*a*/C12*a* diastereomers): To a stirred solution of compound (+)-**14** (1.60 g, 2.11 mmol, 1.0 equiv, dr ca. 4:1) in THF (100 mL) under argon was added a solution of Ni(acac)₂ (109 mg, 0.424 mmol, 0.2 equiv) in THF (10 mL). The resulting mixture was stirred for five minutes at 25 °C, and then cooled to –78 °C. DMDO (Murray and Singh, 1997) (~0.08 M solution in acetone, 80 mL, ~6.33 mmol, 3.0 equiv) was added dropwise at –78 °C. The reaction mixture was stirred at –78 °C for 3 h, and then quenched by addition of dimethylsulfide (5.0 mL, 4.20 g, 68.0 mmol, 32 equiv), and the mixture was stirred at –78 °C for 15 minutes. Saturated aq. NH₄Cl solution (100 mL) was added, and the mixture was allowed to warm to 25 °C. The resulting mixture was diluted with water (150 mL) and extracted with EtOAc (3 × 100 mL). The layers were separated, and the organic phase was washed with water (250 mL) and brine (250 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3%→5%→10% acetone in toluene) gave the hydroxylated product (+)-**15** (840 mg, 1.09 mmol, 52% yield, 72% yield brsm, dr ca. 4:1) as an orange powder, and recovered starting material (+)-**14** (448 mg, 591 μmol, 30% yield). (+)-**15**:

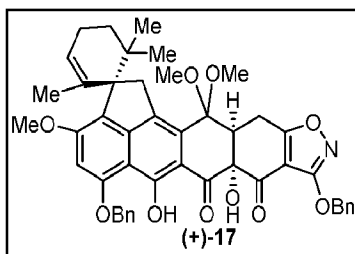
$[\alpha]_D^{22} = +116.5$ ($c=0.2$, CH_2Cl_2); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**15**.



- (1*S*,7*a*'*R*,12*a*'*R*)-5',9'-Bis(benzyloxy)-6',7*a*'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8'(7*a*'*H*,12'*H*)-dione (–)-**16** and (1*S*,7*a*'*S*,12*a*'*S*)-5',9'-bis(benzyloxy)-6',7*a*'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8'(7*a*'*H*,12'*H*)-dione (+)-**17** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a solution of alcohol (+)-**15** (770 mg, 1.00 mmol, 1.0 equiv, dr ca. 4:1) in THF (50 mL) at –78 °C was added dropwise a solution of NaCNBH₃ (252 mg, 4.00 mmol, 4.0 equiv) in THF (12 mL). The reaction mixture was stirred at –78 °C for 1.5 h, then quenched by addition of saturated aq. NH₄Cl solution (30 mL) and allowed to warm to 25 °C. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by preparative TLC (silica gel, 10% acetone in toluene) to give naphthol (+)-**17** (376 mg, 0.470 mmol, 47% yield) and its diastereoisomer (–)-**16** (96.0 mg, 0.120 mmol, 12% yield) both as yellow powders.



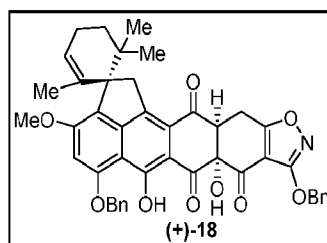
- (1*S*,7*a*'*R*,12*a*'*R*)-5',9'-Bis(benzyloxy)-6',7*a*'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12*a*',13'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8'(7*a*'*H*,12'*H*)-dione (–)-**16**: $[\alpha]_D^{22} = -101$ ($c=0.2$, CH_2Cl_2); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (+)-**16**.



(1S,7a'S,12a'S)-5',9'-Bis(benzyloxy)-6',7a'-dihydroxy-3',13',13'-trimethoxy-2,6,6-trimethyl-12a',13'-dihydro-1'H-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-d][1,2]oxazole]-7',8'-

(7a'H,12'H)-dione (+)-17: $[\alpha]_D^{22} = +71$ ($c=0.2$, CH_2Cl_2); all other physical and spectroscopic data of this

5 compound were identical to those mentioned above for compound (–)-17.

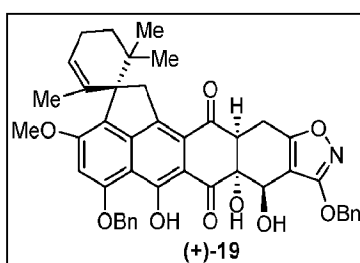


(1S,7a'S,12a'S)-5',9'-Bis(benzyloxy)-6',7a'-dihydroxy-3'-methoxy-2,6,6-trimethyl-12',12a'-dihydro-1'H-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-d][1,2]oxazole]-7',8',13'(7a'H)-

trione (+)-18 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a stirred solution of ketal (+)-17 (230 mg, 290 μmol , 1.0 equiv) in THF (23 mL) was added 2 N aq. HCl (2.5 mL). The reaction mixture was stirred at 25 °C for 5 h and was then diluted with water (50 mL) and extracted with EtOAc (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), and then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give essentially pure triketone (+)-18 (210 mg, 290 μmol , quant. yield) as a yellow foam.

(+)-18: $[\alpha]_D^{22} = +28$ ($c=0.1$, CH_2Cl_2); all other physical and spectroscopic data of this compound were identical

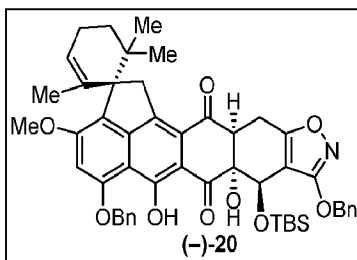
15 to those mentioned above for compound (–)-18.



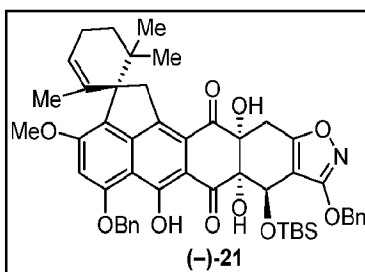
(1S,7a'R,8'R,12a'S)-5',9'-Bis(benzyloxy)-6',7a',8'-trihydroxy-3'-methoxy-2,6,6-trimethyl-7a',8',12',12a'-tetrahydro-1'H-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-d][1,2]oxazole]-

7',13'-dione (+)-19 (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a stirred solution of triketone (+)-18 (196 mg, 280 μmol , 1.0 equiv) in anhydrous EtOAc:acetone (1:1, 20 mL) at 25 °C was added sodium triacetoxyborohydride (68.0 mg, 336 μmol , 1.2 equiv) and the solution was warmed to 40 °C for 2 h. The reaction mixture was then allowed to cool to 25 °C, diluted with water (30 mL) and extracted with EtOAc (30 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 10% acetone in toluene) to

give dihydroxy naphthol (+)-**19** (92.2 mg, 126 μ mol, 47% yield) as a yellow foam. (+)-**19**: $[\alpha]_{\text{D}}^{22} = +6$ ($c=0.1$, CH_2Cl_2); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**19**.



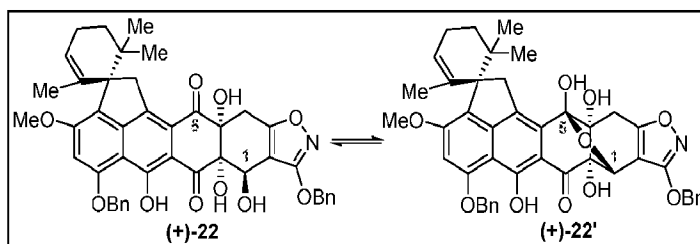
- 5 (1*S*,7*a'**R*,8'*R*,12*a'**S*)-5',9'-Bis(benzyloxy)-8'-[*tert*-butyl(dimethyl)silyl]oxy}-6',7*a'*-dihydroxy-3'-methoxy-2,6,6-trimethyl-7*a'*,8',12',12*a'*-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (–)-**20** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a stirred solution of dihydroxy naphthol (+)-**19** (65.5 mg, 90.0 μ mol, 1.0 equiv) in CH_2Cl_2 (3.3 mL) was added freshly distilled 2,6-lutidine (160 μ L, 1.35 mmol, 15 equiv). The reaction mixture was cooled to 0 °C, and freshly
- 10 distilled TBSOTf (200 μ L, 900 μ mol, 10 equiv) was added. The reaction mixture was allowed to warm to 25 °C and stirred for 15 minutes. Three additional portions of 2,6-lutidine (160 μ L, each) and TBSOTf (200 μ L, each) were added to the reaction flask in 15 minute intervals (0 °C to 25 °C) and the mixture was stirred for an additional 1 h at 25 °C. The reaction was then quenched by addition of saturated aq. NaHCO_3 solution (10 mL) (vigorous bubbling) and extracted with CH_2Cl_2 (2 $\times$ 10 mL). The combined organic phases were dried over
- 15 Na_2SO_4 , filtered, and concentrated under reduced pressure. Residual volatiles were azeotropically removed with toluene (twice). The crude material was then purified by preparative TLC (silica gel, 5% acetone in toluene) to give TBS-ether (–)-**20** (57.3 mg, 68.2 μ mol, 75% yield) as a yellow foam. (–)-**20**: $[\alpha]_{\text{D}}^{22} = -67$ ($c=0.1$, CH_2Cl_2); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (+)-**20**.



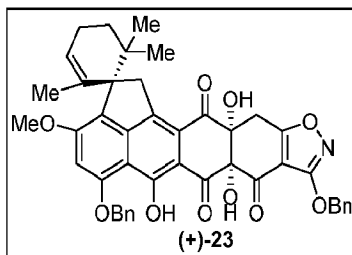
20

- (1*S*,7*a'**S*,8'*R*,12*a'**R*)-5',9'-Bis(benzyloxy)-8'-[*tert*-butyl(dimethyl)silyl]oxy}-6',7*a'*,12*a'*-trihydroxy-3'-methoxy-2,6,6-trimethyl-7*a'*,8',12',12*a'*-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (–)-**21** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): A solution of TBS-ether (–)-**20** (66.5 mg, 79.0 μ mol, 1.0 equiv) in THF (1.4 mL) was cooled to –78 °C, and
- 25 KHMDS solution (1 M in THF, 270 μ L, 270 μ mol, 3.4 equiv) was added dropwise. After stirring for 1 h at –78 °C, freshly prepared recrystallized Davis oxaziridine (Vishwakarma *et al.*, 1988) (80.0 mg, 312 μ mol, 3.9 equiv) in THF (0.4 mL) was added and the mixture was stirred for 2 h at –78 °C. The reaction was quenched by addition of MeOH (0.3 mL), followed by dimethyl sulfide (0.2 mL) and saturated aq. NH_4Cl solution

(3.0 mL). The mixture was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 5% acetone in toluene, then 1.25% acetone in CH₂Cl₂ for the recovered starting material and 5% acetone in CH₂Cl₂ for the product) afforded dihydroxy naphthol (–)-**21** (20.3 mg, 23.7 μmol, 30% yield, 51% yield brsm) as an orange foam and recovered starting material (–)-**20** (27.5 mg, 32.0 μmol, 41% yield). (–)-**21**: $[\alpha]_D^{22} = -28$ ($c=0.1$, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (+)-**21**.

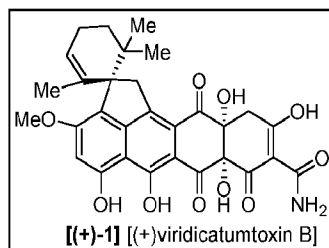


(1*S*,7*a*'*S*,8'*R*,12*a*'*R*)-5',9'-Bis(benzyloxy)-6',7*a*',8',12*a*'-tetrahydroxy-3'-methoxy-2,6,6-trimethyl-7*a*',8',12',12*a*'-tetrahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',13'-dione (+)-**22**/(1*S*,7*a*'*S*,8'*R*,12*a*'*R*,13'*R*)-5',9'-bis(benzyloxy)-6',7*a*',12*a*',13'-tetrahydroxy-3'-methoxy-2,6,6-trimethyl-1',7*a*',8',12',12*a*',13'-hexahydro-7'*H*-spiro[cyclohex-2-ene-1,2'-[11,14]dioxo[10]aza[8,13]epoxycyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazol]-7'-one (+)-**22'** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Dihydroxy naphthol (–)-**21** (11.7 mg, 13.6 μmol, 1.0 equiv) was dissolved in MeCN (0.4 mL) in a plastic vial and cooled to 0 °C. HF·pyridine (70% HF in pyridine, 0.02 mL) was added while stirring and the mixture was warmed to 55 °C. After 2 h, 8 h, and 14 h, an additional portion of HF·pyridine (70% HF in pyridine, 0.05 mL each ; 0 to 55 °C) was added. After 20 h the reaction mixture was allowed to cool to 25 °C, diluted with EtOAc (5 mL), and carefully quenched by addition of saturated aq. NaHCO₃ solution (5 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 20% acetone in toluene) afforded triol (+)-**22**/(+)-**22'** (7.5 mg, 10 μmol, 74% yield) as a yellow foam. $[\alpha]_D^{22} = +44$ ($c=0.1$, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**22**/(–)-**22'**.



(1*S*,7*a*'*S*,12*a*'*R*)-5',9'-Bis(benzyloxy)-6',7*a*',12*a*'-trihydroxy-3'-methoxy-2,6,6-trimethyl-12',12*a*'-dihydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[6,7]tetraceno[2,3-*d*][1,2]oxazole]-7',8',13'(7*a*'*H*)-trione (+)-**23** (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): To a stirred solution of triol (+)-**22**/(+)-**22'** (7.1 mg, 9.5 μmol, 1.0 equiv) in DCE (0.5 mL) that was cooled to 0 °C was added Dess–Martin periodinane (Dess *et al.*, 1983) (0.3 M solution in CH₂Cl₂, 37 μL, 4.6 mg, 11 μmol, 1.2 equiv). After stirring for 30 min at 0 °C, the mixture

was stirred at 25 °C for 1.5 h. The reaction mixture was then warmed up to 50 °C, and one additional portion of Dess–Martin periodinane (0.3 M solution in CH₂Cl₂, 19 μL, 2.4 mg, 5.5 μmol, 0.6 equiv, 0 °C to 50 °C) was added after 1 h. After 2 h at 50 °C, TLC analysis indicated complete conversion. The reaction mixture was allowed to cool to 25 °C, and the reaction was then quenched by addition of saturated aq. NaHCO₃:saturated aq. Na₂S₂O₃ solution (1:1, 10 mL). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2×10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by preparative TLC (silica gel, 5% acetone in CH₂Cl₂) afforded triketone (+)-**23** (5.9 mg, 8.0 μmol, 83% yield) as a yellow powder. (+)-**23**: [α]_D²² = +108 (*c* = 0.1, CH₂Cl₂); all other physical and spectroscopic data of this compound were identical to those mentioned above for compound (–)-**23**.



(1*S*,7*a'S*,11*a'R*)-5',6',7*a'*,10',11*a'*-Pentahydroxy-3'-methoxy-2,6,6-trimethyl-7',8',12'-trioxo-7',7*a'*,8',11',11*a'*,12'-hexahydro-1'*H*-spiro[cyclohex-2-ene-1,2'-cyclopenta[*de*]tetracene]-9'-carboxamide {synthetic (+)-viridicatumtoxin B [(+)-1]} (Nicolaou *et al.*, 2013; Nicolaou *et al.*, 2014): Triketone (+)-**23** (5.3 mg, 7.1 μmol, 1.0 equiv) was dissolved in anhydrous 1,4-dioxane:MeOH (1:1, 1.2 mL) under argon and Pd black (3.7 mg, 35 μmol, 4.9 equiv) was added. The suspension was degassed, placed under a hydrogen atmosphere, and stirred for 10 minutes at 25 °C, after which time the hydrogen was removed by flushing the flask with argon. The suspension was then filtered (Celite®; MeOH:CH₂Cl₂ 1:9), and concentrated under reduced pressure to give crude triketone (+)-viridicatumtoxin B [(+)-**1**, 5.6 mg]. This product was purified by reverse-phase preparative HPLC (Shimadzu HPLC, Atlantis prep T3 OBD column, 16×150 mm, 5 μm particle size, 5 mL/min, 85% MeCN in H₂O + 0.07% TFA buffer, λ = 220 nm: *t* = 10.642 min) to provide pure (+)-viridicatumtoxin B [(+)-**1**, 3.8 mg, 6.8 μmol, 95% yield] as a yellow powder. (+)-**1**: [α]_D²² = +118 (*c* = 0.1, EtOH); all other physical and spectroscopic data of this compound were identical to those mentioned above for (–)-viridicatumtoxin B [(–)-**1**].

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this disclosure have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the disclosure. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the disclosure as defined by the appended claims.

VI. References

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference:

U.S. Patent No. 5,739,169

U.S. Patent No. 5,801,005

U.S. Patent No. 5,824,311

U.S. Patent No. 5,830,880

U.S. Patent No. 5,846,945

WO 2009/008906

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CCDC 1447911 contains the supplementary crystallographic data of 6a for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

CCDC 1503479 contains the supplementary crystallographic data of 11 for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

CCDC 1503480 contains the supplementary crystallographic data of 25 for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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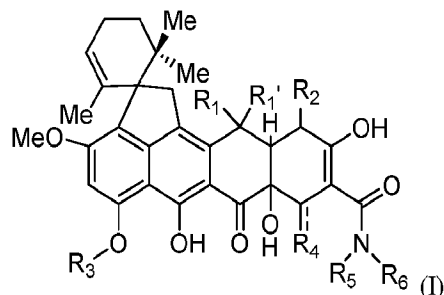
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CLAIMS

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

R_1 and R_1' are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and R_1' are taken together and are oxo;

R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is hydrogen or a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

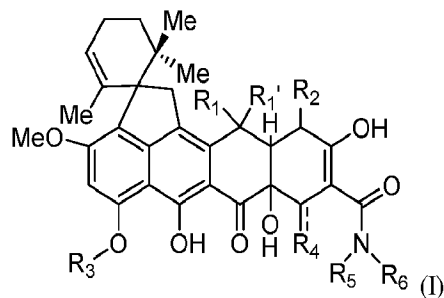
R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

provided that when R_2 is hydrogen and R_3 is hydrogen or methyl, then R_1 is not methoxy or R_1 and R_1' are not oxo;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 further defined as:



wherein:

R_1 and R_1' are each independently alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8);

R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is hydrogen or a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

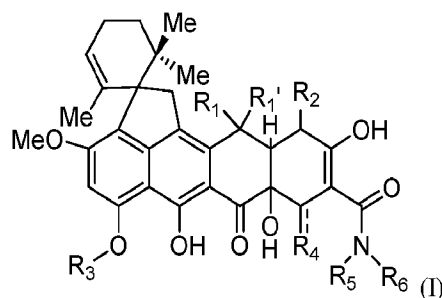
R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 further defined as:



wherein:

R_1 and R_1' are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and R_1' are taken together and are oxo;

R_2 is amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is hydrogen or a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

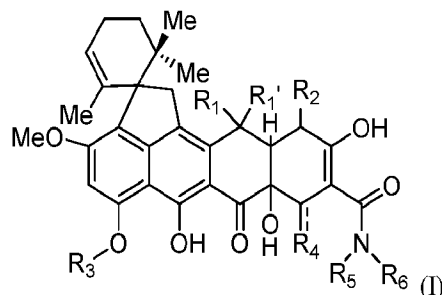
R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 further defined as:



wherein:

R_1 and $R_{1'}$ are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and $R_{1'}$ are taken together and are oxo;

R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

R_7 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

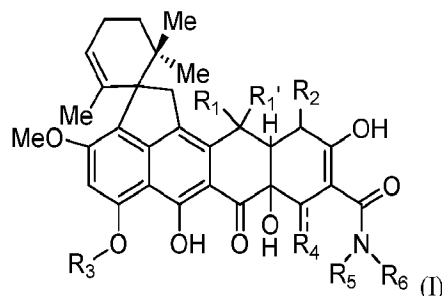
R_4 is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R_5 and R_6 are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

provided that when R_2 is hydrogen and R_3 is methyl, then R_1 is not methoxy or R_1 and $R_{1'}$ are not oxo;

or a pharmaceutically acceptable salt thereof.

5. The compound of either claim 1 or claim 4 further defined as:



wherein:

R_1 and $R_{1'}$ are each independently hydrogen, hydroxy, alkoxy_(C≤8), substituted alkoxy_(C≤8), acyloxy_(C≤8), or substituted acyloxy_(C≤8); or R_1 and $R_{1'}$ are taken together and are oxo;

R_2 is hydrogen, amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), or substituted dialkylamino_(C≤12);

R_3 is a group of the formula: $-Y-R_7$, wherein:

Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

R₇ is amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12);

R₄ is hydroxy, oxo, alkoxy_(C≤8), or substituted alkoxy_(C≤8); and

R₅ and R₆ are each independently hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

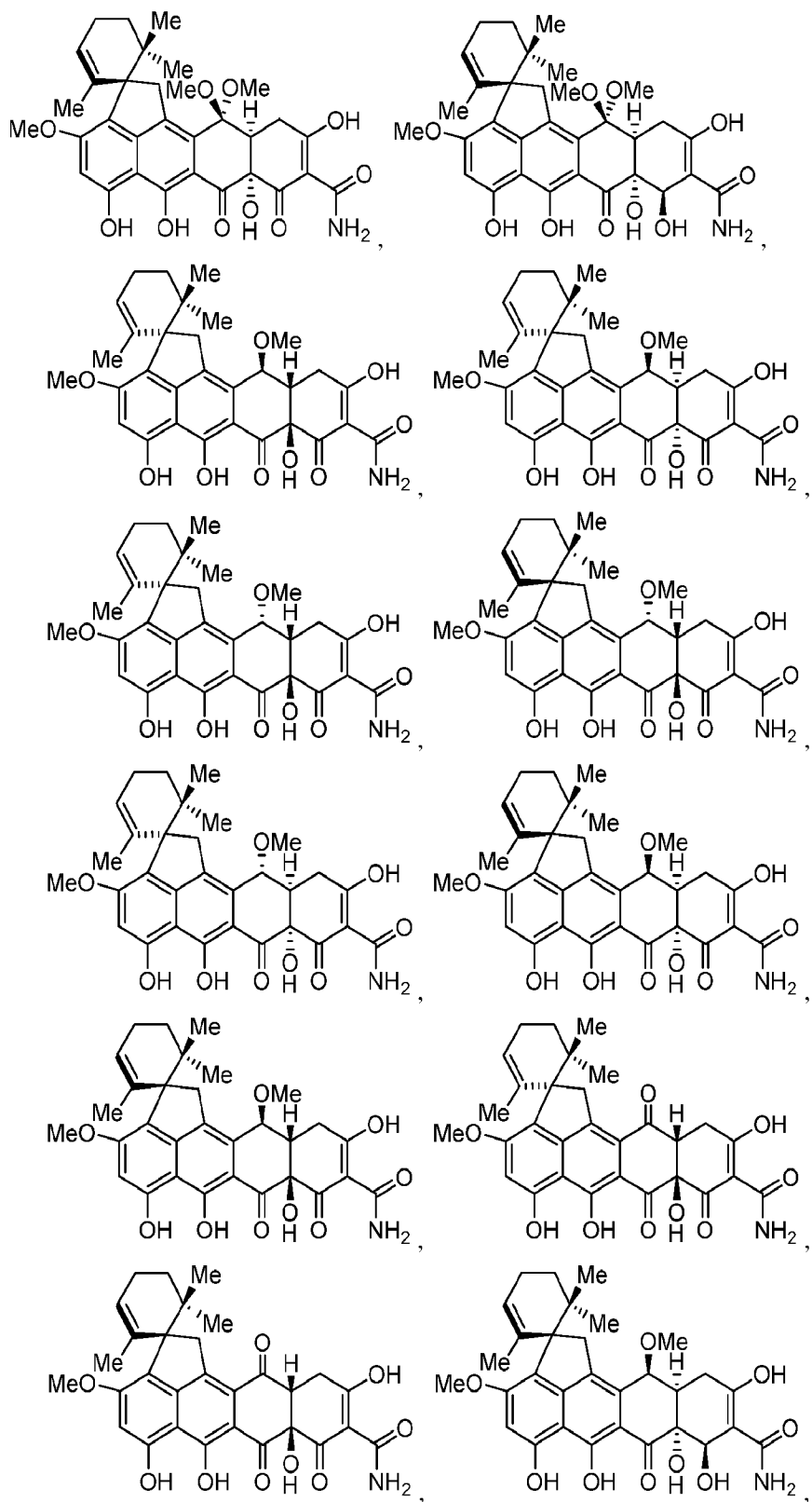
6. The compound according to any one of claims 1 and 3-5, wherein R₁ and R₁' are taken together and are oxo.
7. The compound according to any one of claims 1-5, wherein R₁ is alkoxy_(C≤6) or substituted alkoxy_(C≤6).
8. The compound according to any one of claims 1 and 3-5, wherein R₁ is hydrogen.
9. The compound according to any one of claims 1-5, wherein R₁' is alkoxy_(C≤6) or substituted alkoxy_(C≤6).
10. The compound according to any one of claims 1 and 3-5, wherein R₁' is hydrogen.
11. The compound according to any one of claims 1, 2, 4, and 5, wherein R₂ is hydrogen.
12. The compound according to any one of claims 1-5, wherein R₂ is dialkylamino_(C≤8) or substituted dialkylamino_(C≤8).
13. The compound according to any one of claims 1-3, wherein R₃ is hydrogen.
14. The compound according to any one of claims 1-5, wherein R₃ is -Y-R₇, wherein:

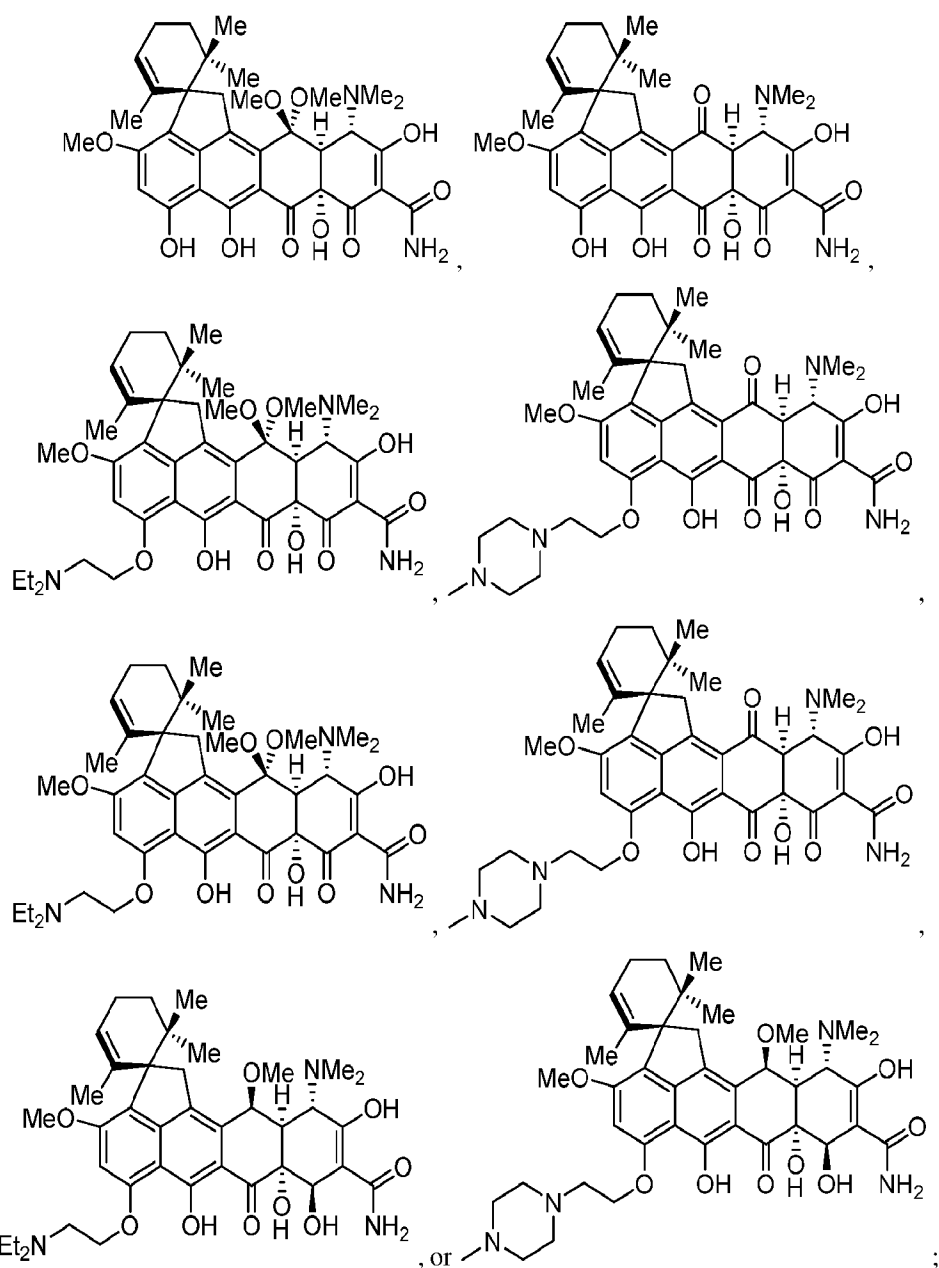
Y is alkanediyl_(C≤8) or substituted alkanediyl_(C≤8); and

R₇ is amino, alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤12), substituted dialkylamino_(C≤12), heterocycloalkyl_(C≤12), or substituted heterocycloalkyl_(C≤12).

15. The compound of claim 14, wherein Y is alkanediyl_(C≤6) or substituted alkanediyl_(C≤6).
16. The compound of claim 14, wherein R₇ is dialkylamino_(C≤12) or substituted dialkylamino_(C≤12).
17. The compound of claim 14, wherein R₇ is heterocycloalkyl_(C≤12) or substituted heterocycloalkyl_(C≤12).
18. The compound according to any one of claims 1-5, wherein R₄ is hydroxy.
19. The compound according to any one of claims 1-5, wherein R₄ is oxo.
20. The compound according to any one of claims 1-5, wherein R₅ is hydrogen.
21. The compound according to any one of claims 1-5, wherein R₆ is hydrogen.
22. The compound according to any one of claims 1-5, wherein the compound is present as greater than 80% of a single stereoisomer.
23. The compound of claim 22, wherein the compound is present as greater than 90% of a single stereoisomer.

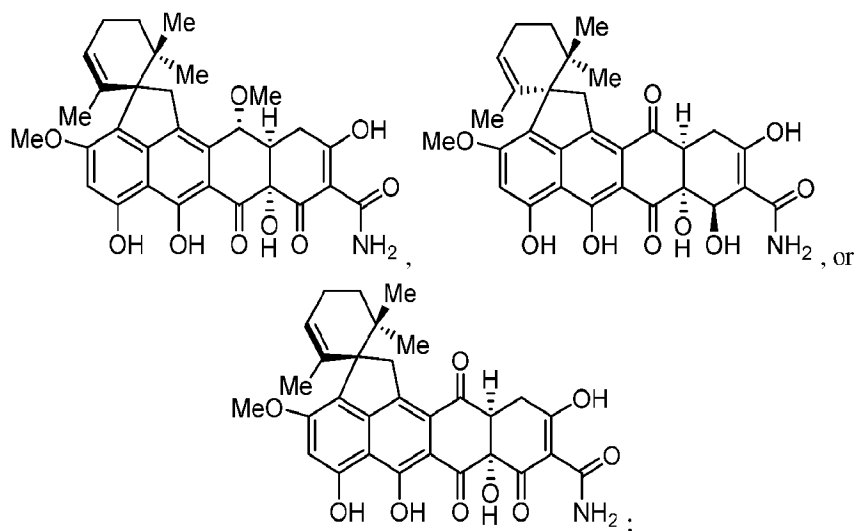
24. The compound of claim 23, wherein the compound is present as greater than 95% of a single stereoisomer.
25. The compound according to any one of claims 1-5 further defined as:





or a pharmaceutically acceptable salt thereof.

26. A compound of the formula:



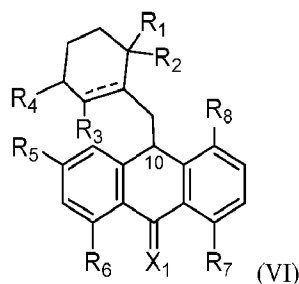
or a pharmaceutically acceptable salt thereof;

wherein the compound is enantiomerically enriched such that the compound is present as at least 80% of the depicted stereoisomer.

27. The compound of claim 26, wherein the compound is present as at least 90% of the depicted stereoisomer.
28. The compound of claim 27, wherein the compound is present as at least 95% of the depicted stereoisomer.
29. A pharmaceutical composition comprising:
- (A) a compound according to any one of claims 1-28; and
 - (B) an excipient.
30. The pharmaceutical composition of claim 29, wherein the pharmaceutical composition is formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion.
31. The pharmaceutical composition of either claim 29 or claim 30, wherein the pharmaceutical composition is formulated as a unit dose.
32. A method of treating a disease or disorder comprising administering a pharmaceutically effective amount of a compound or composition according to any one of claims 1-31.
33. The method of claim 32, wherein the disease or disorder is a microbial infection.
34. The method of either claim 32 or claim 33, wherein the microbial infection is a bacterial infection.

35. The method according to any one of claims 32-34, wherein the infection is by a Gram-positive or Gram-negative bacteria.
36. The method according to any one of claims 32-35, wherein the disease is a bacteria infection by *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Escherichia coli*, *Acinetobacter calcoaceticus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Candida albicans*, *Salmonella typhimurium*, *Streptococcus pneumoniae*, *Micrococcus luteus*, *Bacillus cereus*, or *Bacillus subtilis*.
37. The method of claim 36, wherein the disease is a bacteria infection by *Staphylococcus aureus* 503, *Staphylococcus aureus* 209, *Staphylococcus aureus* RN420, methicillin-resistant *Staphylococcus aureus* CCARM 3167, methicillin-resistant *Staphylococcus aureus* 371, methicillin-resistant *Staphylococcus aureus* CCARM 3506, quinolone-resistant *Staphylococcus aureus* CCARM 3505, quinolone-resistant *Staphylococcus aureus* CCARM 3519, *Bacillus subtilis* KCTC 1021, *Bacillus cereus* KCTC 1661, *Micrococcus luteus* KCTC 1056, *Streptococcus pneumoniae* KCTC 3932, *Streptococcus pneumoniae* KCTC 5412, *Enterococcus faecium* 501, *Enterococcus faecium* KCTC 3122, *Enterococcus faecalis* 5613, *Enterococcus faecalis* KCTC 5191, *Enterococcus faecalis* KCTC 3511, *Staphylococcus epidermidis* KCTC 3958, *Salmonella typhimurium* KCTC 1926, *Acinetobacter calcoaceticus* KCTC 2357, *Escherichia coli* CCARM 1358, *Escherichia coli* KCTC 1682, *Pseudomonas aeruginosa* KCTC 2004, *Pseudomonas aeruginosa* KCTC 2742, *Klebsiella aerogenes* KCTC 2619, *Acinetobacter baumannii* AB210, or *Candida albicans* KCTC 7535.
38. The method according to any one of claim 34-37, wherein the bacteria is a drug-resistant bacteria.
39. The method according to any one of claims 32-38 further comprising administering a second therapeutic agent.
40. The method of claim 39, wherein the second therapeutic agent is an antibiotic.
41. The method of either claim 39 or claim 40, wherein the second therapeutic agent is a tetracycline antibiotic.
42. The method according to any one of claims 39-41, wherein the second therapeutic agent is viridicatumtoxin A, viridicatumtoxin B, vancomycin, tetracycline, spirohexaline, minocycline, tigecycline, doxycycline, a β -lactam antibiotic, an aminoglycoside antibiotic, a sulfonamide antibiotic, a macrolide antibiotic, a glycopeptide antibiotic, an ansamycin antibiotic, an oxazolidinone antibiotic, a quinolone antibiotic, a streptogramin antibiotic, or a lipopeptide antibiotic.
43. The method of either claim 32 or claim 33, wherein the microbial infection is a viral infection.
44. The method according to any one of claims 32, 33, and 43, wherein the virus is a poxvirus.
45. The method of claim 44, wherein the poxvirus is variola virus, vaccinia virus, or molluscum contagiosum.
46. The method according to any one of claims 32, 33, and 43-45 further comprising administering a second therapeutic agent.
47. The method of claim 46, wherein the second therapeutic agent is an interferon or antiviral compound.
48. The method of claim 32, wherein the disease or disorder is cancer.
49. The method of either claim 32 or claim 48, wherein the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.

50. The method of either claim 32 or claim 48, wherein the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, gastrointestinal tract, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.
51. The method according to any one of claims 32 or 48-50 further comprising administering a second therapeutic agent.
52. The method of claim 51, wherein the second therapeutic agent is a second chemotherapeutic agent, radiotherapy, immunotherapy, or surgery.
53. A method of inhibiting the activity of a bacterial ribosome for the treatment of a disease or disorder comprising administering a compound or composition according to any one of claims 1-31.
54. A method of inhibiting the activity of a bacterial UPP synthase for the treatment of a disease or disorder comprising administering a compound or composition according to any one of claims 1-31.
55. A method of preparing a compound of the formula:



wherein:

R_1 , R_2 , and R_3 are each independently hydrogen, $\text{alkyl}_{(C \leq 8)}$, substituted $\text{alkyl}_{(C \leq 8)}$, $\text{cycloalkyl}_{(C \leq 8)}$, or substituted $\text{cycloalkyl}_{(C \leq 8)}$;

R_4 is hydroxy, $\text{alkylsilyloxy}_{(C \leq 18)}$, substituted $\text{alkylsilyloxy}_{(C \leq 18)}$, $\text{alkylarylsilyloxy}_{(C \leq 18)}$, substituted $\text{alkylarylsilyloxy}_{(C \leq 18)}$, $\text{alkylaralkylsilyloxy}_{(C \leq 18)}$, substituted $\text{alkylaralkylsilyloxy}_{(C \leq 18)}$, or $-\text{OR}_a$, wherein:

R_a is a hydroxy protecting group;

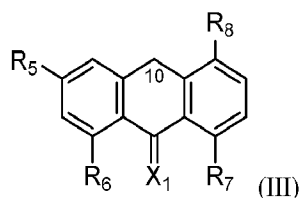
R_5 , R_6 , R_7 , and R_8 are each independently hydroxy, $\text{alkoxy}_{(C \leq 12)}$, substituted $\text{alkoxy}_{(C \leq 12)}$, $\text{alkenyloxy}_{(C \leq 12)}$, substituted $\text{alkenyloxy}_{(C \leq 12)}$, $\text{alkynyloxy}_{(C \leq 12)}$, substituted $\text{alkynyloxy}_{(C \leq 12)}$, $\text{aryloxy}_{(C \leq 12)}$, substituted $\text{aryloxy}_{(C \leq 12)}$, $\text{aralkoxy}_{(C \leq 12)}$, substituted $\text{aralkoxy}_{(C \leq 12)}$, or $-\text{OR}_b$, wherein:

R_b is a hydroxy protecting group;

X_1 is O or NR_c , wherein:

R_c is hydrogen, $\text{alkyl}_{(C \leq 18)}$, or substituted $\text{alkyl}_{(C \leq 18)}$;

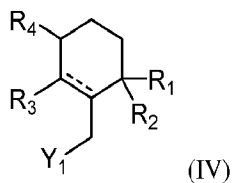
comprising reacting a compound of the formula:



wherein:

R₅, R₆, R₇, and R₈ are as defined above;

with a compound of the formula:



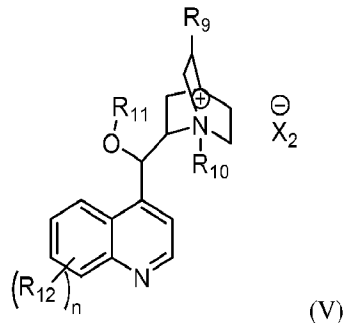
wherein:

R₅, R₆, R₇, and R₈ are as defined above;

Y₁ is a leaving group;

in the presence of a phase transfer catalyst and a base under conditions sufficient to cause a reaction.

56. The method of claim 55, wherein the phase transfer catalyst is a compound of the formula:



wherein:

R₉ is alkyl_(C≤8), alkenyl_(C≤8), or a substituted version of either of these groups;

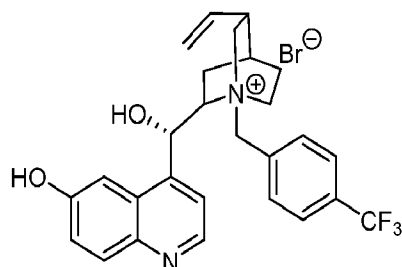
R₁₀ and R₁₁ are each independently alkyl_(C≤18), alkenyl_(C≤18), aryl_(C≤18), aralkyl_(C≤18), or a substituted version of any of these groups;

R₁₂ is hydrogen, hydroxy, alkoxy_(C≤12), substituted alkoxy_(C≤12), acyloxy_(C≤12), substituted acyloxy_(C≤12), aralkyl_(C≤12), or substituted aralkyl_(C≤12);

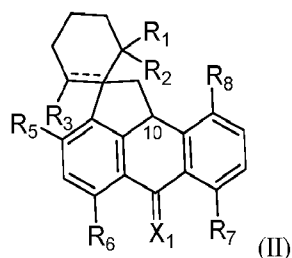
X₂ is a monovalent anion; and

n is 1, 2, or 3.

57. The method of claim 56, wherein the phase transfer catalyst is a compound of the formula:



58. The method according to any one of claims 55-57, wherein the base is a metal carbonate.
59. The method of claim 58, wherein the base is cesium carbonate.
60. The method according to any one of claims 55-57, wherein the method comprises adding the base as a solution in water.
61. The method of claim 60, wherein the base as a solution in water comprises 20% to about 60% base.
62. The method of claim 61, wherein the base as a solution in water comprises 40% base.
63. The method according to any one of claims 55-57, wherein the method comprises adding from about 5 equivalents to about 25 equivalents of the base relative to the compound of formula III.
64. The method of claim 63, wherein the method comprises adding about 10 equivalents of the base.
65. The method according to any one of claims 55-57, wherein the method comprises adding from about 1.0 equivalents to about 5 equivalents of the compound of formula IV relative to the compound of formula III.
66. The method of claim 65, wherein the method comprises adding about 1.1 equivalents of the compound of formula IV.
67. The method according to any one of claims 55-57, wherein the method comprises adding from about 0.1 mol% to about 20 mol% of the phase transfer catalyst.
68. The method of claim 67, wherein the method comprises adding from about 0.1 mol% to about 5 mol% of the phase transfer catalyst.
69. The method according to any one of claims 55-57, wherein the method further comprises an organic solvent.
70. The method of claim 69, wherein the organic solvent is a haloalkane_(C₁₋₈).
71. The method of claim 70, wherein the organic solvent is dichloroethane or methylene chloride.
72. The method according to any one of claims 55-57, wherein the method further comprises reacting at a temperature from about -80 °C to about 25 °C.
73. The method of claim 72, wherein the temperature is from about -40 °C to about 0 °C.
74. The method according to any one of claims 55-57, wherein the method comprises reacting for a time period from about 6 hours to about 1 week.
75. The method of claim 74, wherein the time period is about 1 day to about 4 days.
76. The method according to any one of claims 55-57, wherein the method further comprises reacting the compound of formula II with a fluoride source to produce a compound of formula:



wherein:

R_1 , R_2 , and R_3 are each independently hydrogen, $\text{alkyl}_{(C \leq 8)}$, substituted $\text{alkyl}_{(C \leq 8)}$, $\text{cycloalkyl}_{(C \leq 8)}$, or substituted $\text{cycloalkyl}_{(C \leq 8)}$;

R_5 , R_6 , R_7 , and R_8 are each independently hydroxy, $\text{alkoxy}_{(C \leq 12)}$, substituted $\text{alkoxy}_{(C \leq 12)}$, $\text{alkenyloxy}_{(C \leq 12)}$, substituted $\text{alkenyloxy}_{(C \leq 12)}$, $\text{alkynyloxy}_{(C \leq 12)}$, substituted $\text{alkynyloxy}_{(C \leq 12)}$, $\text{aryloxy}_{(C \leq 12)}$, substituted $\text{aryloxy}_{(C \leq 12)}$, $\text{aralkoxy}_{(C \leq 12)}$, substituted $\text{aralkoxy}_{(C \leq 12)}$, or $-\text{OR}_b$, wherein:

R_b is a hydroxy protecting group;

X_1 is O or NR_c , wherein:

R_c is hydrogen, $\text{alkyl}_{(C \leq 18)}$, or substituted $\text{alkyl}_{(C \leq 8)}$;

or a salt thereof.

77. The method according to any one of claims 55-76, further comprising a purification step.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/19216

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-12, 14-25, 29-54 and 77
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/19216

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/65; C07C 235/82 (2017.01)

CPC - C07C235/82; A61K31/65

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/014643 A1 (WILLIAM MARSH RICE UNIVERSITY) 28 January 2016 (28.01.2016) pg 6, ln 1-24; pg 67, ln 13-14; pg 71, ln 8 -10; pg 73, Table 1	1-5, 13, 26-28
Y	NICOLAOU et al. 'Total Synthesis of Viridicatumtoxin B and Analogues Thereof: Strategy Evolution, Structural Revision, and Biological Evaluation', J. Am. Chem. Soc. 2014, Vol.136, pp. 12137-12160. pg 12146, col 1, para 2 to col 2, para 1; Scheme 17	55-76
Y	US 2013/0274483 A1 (SUN et al.) 17 October 2013 (17.10.2013) para [0172], [0184], [0190]-[0192], [0198], [0234]-[0235]	55-76
Y	US 5,274,117 A (LEE et al.) 28 December 1993 (28.12.1993) col 5, ln 50 to col 6, ln 30; col 9, ln 6-55	57, (58-76)/57

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search

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Date of mailing of the international search report

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