(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2024 (19.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/259342 A2

(51) International Patent Classification:
Not classified

(21) International Application Number:
PCT/US2024/034160

(22) International Filing Date:
14 June 2024 (14.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/508,459 15 June 2023 (15.06.2023) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: METHODS FOR SYNTHESIZING ALPHA-DEUTERATED ALPHA-AMINO ACIDS AND DERIVATIVES THEREOF

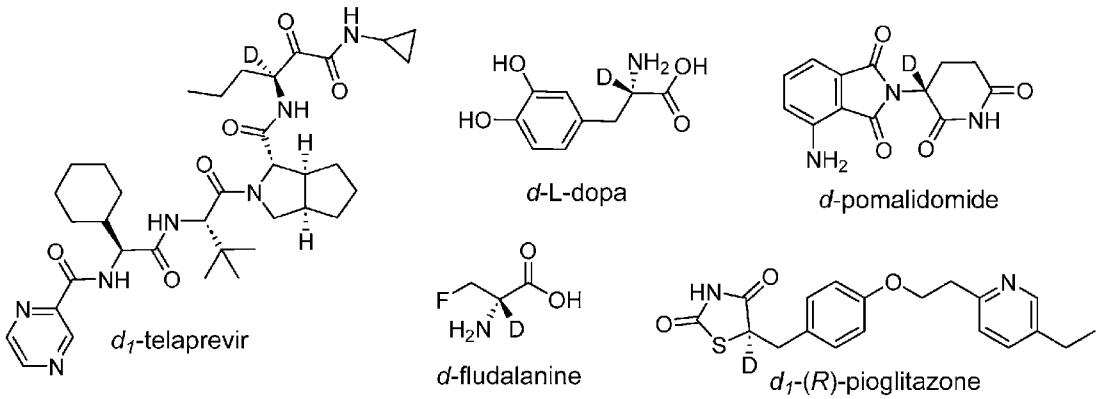

FIG. 1

(57) Abstract: Exemplary materials, methods and techniques disclosed and contemplated herein generally relate to methods for synthesizing α-deuterated α-amino acids and their derivatives.

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METHODS FOR SYNTHESIZING ALPHA-DEUTERATED ALPHA-AMINO ACIDS AND DERIVATIVES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/508,459, filed on June 15, 2023, the entire contents of which are incorporated herein by reference.

STATEMENT OF GOVERNMENT INTEREST

[0002] This invention was made with government support under Grant No. 5R01GM125920-03, awarded by the National Institute of Health (NIH). The government has certain rights in the invention.

TECHNICAL FIELD

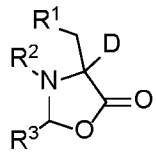
[0003] Exemplary materials, methods and techniques disclosed and contemplated herein generally relate to methods for synthesizing α-deuterated α-amino acids and their derivatives.

INTRODUCTION

[0004] The current methods for synthesizing α-deuterated α-amino acid derivatives employ the asymmetric alkylation of glycine derived imines followed by deuteration with D_2O or H/D exchange of amino acid derivatives. However, these existing methods only achieve moderate deuteration levels, and do not work well for highly sterically demanding amino acids.

SUMMARY

[0005] In one aspect, the present disclosure provides a method for preparing a deuterated compound of formula (I), or a salt thereof,



(I),

wherein:

R^1 is G^1, $C_{1\text{-}10}$alkyl, $–L^1–R^Y$, or $–G^1\text{-}L^1–R^Y$;

R^2 is an amine protecting group, hydrogen, or C_{1-6}alkyl; and

R^3 is C_{1-6}alkyl or C_{1-4}haloalkyl;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, –OC_{1-6}alkyl, –OG^{1a}, –OC_{1-4}haloalkyl, –SH, –SC_{1-6}alkyl, –SG^{1a}, –SC_{1-4}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –NHG^{1a}, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)G^{1a}, –C(O)OC_{1-4}alkyl, –C(O)OG^{1a}, –C(O)NH_2, –C(O)NHG^{1a}, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2G^{1a}, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, –SO_2N(C_{1-4}alkyl)$_2$, –C_{1-4}alkylene–OH, –C_{1-4}alkylene–OC_{1-4}alkyl, –C_{1-4}alkylene–NH_2, –C_{1-4}alkylene–NHC_{1-4}alkyl, –C_{1-4}alkylene–N(C_{1-4}alkyl)$_2$, –O–C_{1-4}alkylene–OH, –O–C_{1-4}alkylene–OC_{1-4}alkyl, –O–C_{1-4}alkylene–NH_2, –O–C_{1-4}alkylene–NHC_{1-4}alkyl, –O–C_{1-4}alkylene–N(C_{1-4}alkyl)$_2$, and C_{1-3}alkylene–G^{1a}, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –SO_2N(C_{1-4}alkyl)$_2$;

L^1, at each occurrence, is a C_{1-10}alkylene, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with –O–, –S–, –SO–, –SO_2–, –C(O)–, –C(O)O–, –C(O)N(R^X)–, or –N(R^X)–, wherein 2 methylene groups replaced with –O–, –S–, –SO–, –C(O)O–, –C(O)N(R^X)–, –SO_2–, or –N(R^X)– are separated by two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with –Cy^1–;

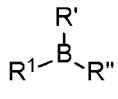
Cy^1 is phenylene, C_{3-6}cycloalkylene, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, and halogen;

R^X is hydrogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, or $-C_{1-3}$alkylene–C_{3-4}cycloalkyl;

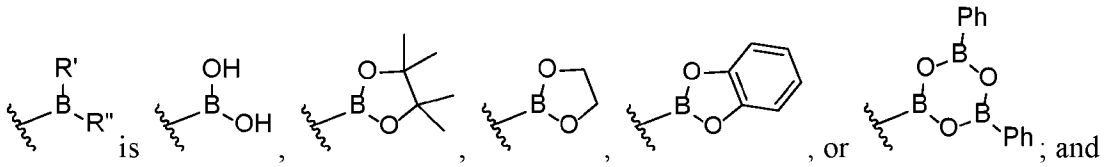
R^Y, at each occurrence, is C_{1-4}alkyl, C_{2-4}alkenyl, $-OC_{1-4}$alkyl, $-OC_{1-4}$haloalkyl, –OH, G^Y, $-OG^Y$, cyano, –SH, $-SC_{1-4}$alkyl, $-SC_{1-4}$haloalkyl, $-SG^1$, $-NH_2$, $-NHC_{1-4}$alkyl, $-NHG^Y$, $-N(C_{1-4}alkyl)_2$, $-NHC(O)C_{1-4}$alkyl, $-NHC(O)OC_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)G^Y$, $-C(O)OG^Y$, $-C(O)OC_{1-4}$alkyl, $-C(O)NH_2$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-C(O)NHG^Y$, $-C(O)N(G^Y)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2G^Y$, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, or $-SO_2N(C_{1-4}alkyl)_2$; and

G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, $-OC_{1-4}$alkyl, $-OC_{1-2}$haloalkyl, –SH, $-SC_{1-4}$alkyl, $-SC_{1-2}$haloalkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-C(O)C_{1-4}$alkyl, $-C(O)OC_{1-4}$alkyl,$-C(O)NH_2$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, and $-SO_2N(C_{1-4}alkyl)_2$.

[0006] The method for preparing a deuterated compound of formula (I), or a salt thereof, may comprise mixing a compound of formula (III):



(III), wherein

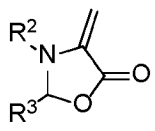


is

, or

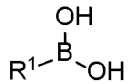
; and

a compound of formula (II),

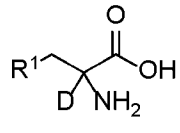


(II),

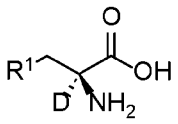
with a photocatalyst, a base, and D_2O to form a reaction mixture; and exposing the reaction mixture to light, thereby producing the deuterated compound of formula (I). The compound of

formula (I) may have at least 75% deuterium incorporation at each deuterium label. The compound of formula (III) may be  . The base may be a Lewis base. The photocatalyst may be an iridium (Ir)-based photocatalyst. The light may be blue LED light.

[0007] In another aspect, the present disclosure provides methods of preparing a deuterated compound of formula (I-AA), or a salt thereof,


(I-AA),

the method comprising preparing a deuterated compound of formula (I), then hydrolyzing the deuterated compound of formula (I). The deuterated compound of formula (I-AA) may be:



[0008] Before any embodiments of the disclosure are explained in detail, it is to be understood that the disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The disclosure is capable of other embodiments and of being practiced or of being carried out in various ways.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 shows examples of α-deuterated amino acid therapeutics.

[0010] FIG. 2 shows an example substrate scope for the deuteration methods described herein.

[0011] FIG. 3 shows an example late-stage functionalization of complex bioactive molecules and conversion of products to amino acids using the deuteration methods described herein.

DETAILED DESCRIPTION

[0012] Described herein is a mild, versatile deuteration method that has been developed for efficient incorporation of various side chains and deuterium into methylene oxazolidinones. The method delivers structurally diverse chiral α-deuterated α-amino acid derivatives in good yields with excellent diastereoselectivity and uniformly high level of deuterium incorporation. The

employment of readily available starting materials, an inexpensive and safe D_2O as deuterium reagent, mild reaction conditions, and operational simplicity makes the method practical in synthesis. Notably, the approach has significantly expanded the scope for accessing both aryl and alkyl side chain contained α-amino acids. It is expected that the synthetic method and the valued deuterated amino acid building blocks will find broad applications in organic and medicinal chemistry.

[0013] Before any embodiments of the disclosure are explained in detail, it is to be understood that the disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The disclosure is capable of other embodiments and of being practiced or of being carried out in various way.

I. Definitions

[0014] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0015] The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments "comprising," "consisting of" and "consisting essentially of," the embodiments or elements presented herein, whether explicitly set forth or not.

[0016] The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier "about" should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression "from about 2 to about 4" also discloses the range "from 2 to 4." The

term "about" may refer to plus or minus 10% of the indicated number. For example, "about 10%" may indicate a range of 9% to 11%, and "about 1" may mean from 0.9–1.1. Other meanings of "about" may be apparent from the context, such as rounding off, so, for example "about 1" may also mean from 0.5 to 1.4.

[0017] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0018] The term "alkoxy," as used herein, refers to a group –O–alkyl. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0019] The term "alkyl," as used herein, means a straight or branched, saturated hydrocarbon chain. The term "lower alkyl" or "$C_{1\text{-}6}$alkyl" means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. The term "$C_{1\text{-}4}$alkyl" means a straight or branched chain hydrocarbon containing from 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

[0020] The term "alkenyl," as used herein, means a straight or branched, hydrocarbon chain containing at least one carbon-carbon double bond.

[0021] The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

[0022] The term "alkylamino," as used herein, means at least one alkyl group, as defined herein, is appended to the parent molecular moiety through an amino group, as defined herein.

[0023] The term "amide," as used herein, means –C(O)NR– or –NRC(O)–, wherein R may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0024] The term "aminoalkyl" as used herein, means at least one amino group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0025] The term "amino," as used herein, means $-NR_xR_y$, wherein R_x and R_y may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl. In the case of an aminoalkyl group or any other moiety where amino appends together two other moieties, amino may be $-NR_x-$, wherein R_x may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0026] The term "aryl," as used herein, refers to a phenyl or a phenyl appended to the parent molecular moiety and fused to a cycloalkane group (e.g., the aryl may be indan-4-yl), fused to a 6-membered arene group (i.e., the aryl is naphthyl), or fused to a non-aromatic heterocycle (e.g., the aryl may be benzo[d][1,3]dioxol-5-yl). The term "phenyl" is used when referring to a substituent and the term 6-membered arene is used when referring to a fused ring. The 6-membered arene is monocyclic (e.g., benzene or benzo). The aryl may be monocyclic (phenyl) or bicyclic (e.g., a 9- to 12-membered fused bicyclic system).

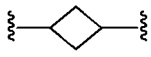
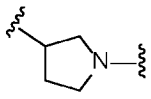
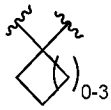
[0027] The term "cyanoalkyl," as used herein, means at least one –CN group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0028] The term "cycloalkoxy," as used herein, refers to a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

[0029] The term "cycloalkyl" or "cycloalkane," as used herein, refers to a saturated ring system containing all carbon atoms as ring members and zero double bonds. The term "cycloalkyl" is used herein to refer to a cycloalkane when present as a substituent. A cycloalkyl may be a monocyclic cycloalkyl (e.g., cyclopropyl), a fused bicyclic cycloalkyl (e.g., decahydronaphthalenyl), or a bridged cycloalkyl in which two non-adjacent atoms of a ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms (e.g., bicyclo[2.2.1]heptanyl). Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, and bicyclo[1.1.1]pentanyl.

[0030] The term "cycloalkenyl" or "cycloalkene," as used herein, means a non-aromatic monocyclic or multicyclic ring system containing all carbon atoms as ring members and at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. The term "cycloalkenyl" is used herein to refer to a cycloalkene when present as a substituent. A cycloalkenyl may be a monocyclic cycloalkenyl (e.g., cyclopentenyl), a fused bicyclic cycloalkenyl (e.g., octahydronaphthalenyl), or a bridged cycloalkenyl in which two non-adjacent atoms of a ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms (e.g., bicyclo[2.2.1]heptenyl). Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl.

[0031] The term "carbocyclyl" means a "cycloalkyl" or a "cycloalkenyl." The term "carbocycle" means a "cycloalkane" or a "cycloalkene." The term "carbocyclyl" refers to a "carbocycle" when present as a substituent.

[0032] The terms cycloalkylene and heterocyclylene refer to divalent groups derived from the base ring, i.e., cycloalkane, heterocycle. For purposes of illustration, examples of cycloalkylene and heterocyclylene include, respectively,  and  . Cycloalkylene and heterocyclylene include a geminal divalent groups such as 1,1-C_{3-6}cycloalkylene (i.e., ). A further example is 1,1-cyclopropylene (i.e., ).

[0033] The term "halogen" or "halo," as used herein, means Cl, Br, I, or F.

[0034] The term "haloalkyl," as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by a halogen.

[0035] The term "haloalkoxy," as used herein, means at least one haloalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom.

[0036] The term "halocycloalkyl," as used herein, means a cycloalkyl group, as defined herein, in which one or more hydrogen atoms are replaced by a halogen.

[0037] The term "heteroalkyl," as used herein, means an alkyl group, as defined herein, in which one or more of the carbon atoms has been replaced by a heteroatom selected from S, O, P

and N. Representative examples of heteroalkyls include, but are not limited to, alkyl ethers, secondary and tertiary alkyl amines, amides, and alkyl sulfides.

[0038] The term "heteroaryl," as used herein, refers to an aromatic monocyclic heteroatom-containing ring (monocyclic heteroaryl) or a bicyclic ring system containing at least one monocyclic heteroaromatic ring (bicyclic heteroaryl). The term "heteroaryl" is used herein to refer to a heteroarene when present as a substituent. The monocyclic heteroaryl are five or six membered rings containing at least one heteroatom independently selected from the group consisting of N, O and S (e.g., 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N). The five membered aromatic monocyclic rings have two double bonds, and the six membered aromatic monocyclic rings have three double bonds. The bicyclic heteroaryl is an 8- to 12-membered ring system and includes a fused bicyclic heteroaromatic ring system (i.e., 10π electron system) such as a monocyclic heteroaryl ring fused to a 6-membered arene (e.g., quinolin-4-yl, indol-1-yl), a monocyclic heteroaryl ring fused to a monocyclic heteroarene (e.g., naphthyridinyl), and a phenyl fused to a monocyclic heteroarene (e.g., quinolin-5-yl, indol-4-yl). A bicyclic heteroaryl/heteroarene group includes a 9-membered fused bicyclic heteroaromatic ring system having four double bonds and at least one heteroatom contributing a lone electron pair to a fully aromatic 10π electron system, such as ring systems with a nitrogen atom at the ring junction (e.g., imidazopyridine) or a benzoxadiazolyl. A bicyclic heteroaryl also includes a fused bicyclic ring system composed of one heteroaromatic ring and one non-aromatic ring such as a monocyclic heteroaryl ring fused to a monocyclic carbocyclic ring (e.g., 6,7-dihydro-5H-cyclopenta[b]pyridinyl), or a monocyclic heteroaryl ring fused to a monocyclic heterocycle (e.g., 2,3-dihydrofuro[3,2-b]pyridinyl). The bicyclic heteroaryl is attached to the parent molecular moiety at an aromatic ring atom. Other representative examples of heteroaryl include, but are not limited to, indolyl (e.g., indol-1-yl, indol-2-yl, indol-4-yl), pyridinyl (including pyridin-2-yl, pyridin-3-yl, pyridin-4-yl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl (e.g., pyrazol-4-yl), pyrrolyl, benzopyrazolyl, 1,2,3-triazolyl (e.g., triazol-4-yl), 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, imidazolyl, thiazolyl (e.g., thiazol-4-yl), isothiazolyl, thienyl, benzimidazolyl (e.g., benzimidazol-5-yl), benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, furanyl, oxazolyl, isoxazolyl, purinyl, isoindolyl, quinoxalinyl, indazolyl (e.g., indazol-4-yl, indazol-5-yl), quinazolinyl, 1,2,4-triazinyl, 1,3,5-

triazinyl, isoquinolinyl, quinolinyl, imidazo[1,2-a]pyridinyl (e.g., imidazo[1,2-a]pyridin-6-yl), naphthyridinyl, pyridoimidazolyl, thiazolo[5,4-b]pyridin-2-yl, and thiazolo[5,4-d]pyrimidin-2-yl.

[0039] The term "heterocycle" or "heterocyclic," as used herein, means a monocyclic heterocycle, a bicyclic heterocycle, or a tricyclic heterocycle. The term "heterocyclyl" is used herein to refer to a heterocycle when present as a substituent. The monocyclic heterocycle is a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. The five-membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The six-membered ring contains zero, one or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. The seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocyclyls include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, 2-oxo-3-piperidinyl, 2-oxoazepan-3-yl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, oxetanyl, oxepanyl, oxocanyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, 1,2-thiazinanyl, 1,3-thiazinanyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to a 6-membered arene, or a monocyclic heterocycle fused to a monocyclic cycloalkane, or a monocyclic heterocycle fused to a monocyclic cycloalkene, or a monocyclic heterocycle fused to a monocyclic heterocycle, or a monocyclic heterocycle fused to a monocyclic heteroarene, or a spiro heterocycle group, or a bridged monocyclic heterocycle ring system in which two non-adjacent atoms of the ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. The bicyclic heterocyclyl is attached to the parent molecular moiety at a non-aromatic ring atom (e.g., indolin-1-yl). Representative examples of bicyclic heterocyclyls include, but are not limited to, chroman-4-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzothien-

2-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2-azaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), azabicyclo[3.1.0]hexanyl (including 3-azabicyclo[3.1.0]hexan-3-yl), 2,3-dihydro-1H-indol-1-yl, isoindolin-2-yl, octahydrocyclopenta[c]pyrrolyl, octahydropyrrolopyridinyl, tetrahydroisoquinolinyl, 7-oxabicyclo[2.2.1]heptanyl, hexahydro-2H-cyclopenta[b]furanyl, 2-oxaspiro[3.3]heptanyl, 3-oxaspiro[5.5]undecanyl, 6-oxaspiro[2.5]octan-1-yl, and 3-oxabicyclo[3.1.0]hexan-6-yl. Tricyclic heterocycles are exemplified by a bicyclic heterocycle fused to a 6-membered arene, or a bicyclic heterocycle fused to a monocyclic cycloalkane, or a bicyclic heterocycle fused to a monocyclic cycloalkene, or a bicyclic heterocycle fused to a monocyclic heterocycle, or a bicyclic heterocycle in which two non-adjacent atoms of the bicyclic ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Examples of tricyclic heterocycles include, but are not limited to, octahydro-2,5-epoxypentalene, hexahydro-2H-2,5-methanocyclopenta[b]furan, hexahydro-1H-1,4-methanocyclopenta[c]furan, aza-adamantane (1-azatricyclo[3.3.1.13,7]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.13,7]decane). The monocyclic, bicyclic, and tricyclic heterocyclyls are connected to the parent molecular moiety at a non-aromatic ring atom.

[0040] The term “hydroxyl” or “hydroxy,” as used herein, means an -OH group.

[0041] The term “hydroxyalkyl,” as used herein, means at least one -OH group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0042] Terms such as "alkyl," "cycloalkyl," "alkylene," etc. may be preceded by a designation indicating the number of atoms present in the group in a particular instance (e.g., "C_{1-4}alkyl," "C_{3-6}cycloalkyl," "C_{1-4}alkylene"). These designations are used as generally understood by those skilled in the art. For example, the representation "C" followed by a subscripted number indicates the number of carbon atoms present in the group that follows. Thus, "C_3alkyl" is an alkyl group with three carbon atoms (i.e., *n*-propyl, isopropyl). Where a range is given, as in "C_{1-4}," the members of the group that follows may have any number of carbon atoms falling within the recited range. A "C_{1-4}alkyl," for example, is an alkyl group having from 1 to 4 carbon atoms, however arranged (i.e., straight chain or branched).

[0043] The term “substituted” refers to a group that may be further substituted with one or more non-hydrogen substituent groups. Substituent groups include, but are not limited to, halogen, =O

(oxo), =S (thioxo), cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycle, cycloalkylalkyl, heteroarylalkyl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkylene, aryloxy, phenoxy, benzyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, –COOH, ketone, amide, carbamate, and acyl.

[0044] For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0045] In the compounds of formulae (I), (I-AA), (II) and any subformulas, any "hydrogen" or "H," whether explicitly recited or implicit in the structure, encompasses hydrogen isotopes ^{1}H (protium) and ^{2}H (deuterium).

[0046] The present disclosure also includes an isotopically-labeled compound (e.g., deuterium labeled), where an atom in the isotopically-labeled compound is specified as a particular isotope of the atom. Examples of isotopes suitable for inclusion in the compounds of the invention are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[0047] The term “isotopically enriched,” as used herein with reference to any particular isotope of any particular atom of a compound, means that in a composition comprising a plurality of molecules of the compound, the amount (e.g., fraction, ration or percentage) of the plurality of molecules having the particular isotope at the particular atom is substantially greater than the natural abundance of the particular isotope, due to synthetic enrichment of the particular atom with the particular isotope.

[0048] Isotopically-enriched forms of compounds of formulae (I), (I-AA), (II), or any subformulas, may generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using an appropriate isotopically-enriched reagent in place of a non-isotopically-enriched reagent. The extent of isotopic enrichment can be characterized as a percent incorporation of a particular isotope at an isotopically labeled atom (e.g., % deuterium incorporation at a deuterium label).

[0049] For example, a compound with an isotopically enriched deuterium (^{2}H, denoted as "D") atom at one or more particular locations includes a plurality of molecules of the compound, where as a result of synthetic enrichment, the percentage of the plurality of molecules having deuterium at each of the one or more particular locations is greater than about 1% (the natural abundance of deuterium is substantially less than 1%), and in many cases is substantially greater than about 1%.

[0050] In some cases, a compound with an isotope incorporated at a particular isotopically labeled atom may include a plurality of molecules of the compound, where the amount of the plurality of molecules having the isotope at the particular isotopically labeled atom may be at least about two-or-more-fold greater than the natural abundance of the isotope at that atom, including but not limited to at least about two-fold, at least about three-fold, at least about four-fold, at least about five-fold, at least about 10-fold, at least about 20-fold, at least about 30-fold, at least about 40-fold, at least about 50-fold, at least about 60-fold, at least about 70-fold, at least about 80-fold, at least about 90-fold, at least about 100-fold, and at least about 200-fold, among others. In some cases, a compound with an isotope at a particular isotopically labeled atom also may include a plurality of molecules of the compound where, as a result of synthetic enrichment, at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.5% of the plurality of molecules have the isotope at the isotopically labeled atom.

[0051] The term "natural abundance," as used herein with reference to any particular isotope of an element, refers to the abundance of the isotope as naturally found on the planet Earth. For example, the natural abundance of ^{15}N on the planet Earth is generally regarded to be about 0.37% (i.e., substantially less than about 1%), while the natural abundance of deuterium (^{2}H) on the planet Earth is generally regarded to be about 0.015% (i.e., substantially less than about 1%).

[0052] The term "photochemical," as used herein, means relating to or caused by the chemical action of light.

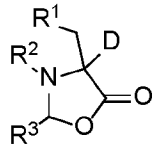
II. Exemplary Compounds

[0053] The present disclosure relates to deuterated amino acids, their derivatives, and methods for synthesizing the same. The importance of the deuterium labelling has been fully demonstrated

by a wide range of applications in chemical, biological and material sciences, such as reaction mechanism studies, drug discovery and development, and molecular structure analysis. Among them, the value of introducing deuterium into the α-position of amino acids and derivatives has been appreciated by the examples of biologically active compounds and therapeutics (**FIG. 1**). The modification can improve the properties such as metabolic stability and slowdown of racemization in peptido and peptidomimetic therapeutics and thus enhance their performance.

A. Deuterated Compounds of Formula (I)

[0054] In one aspect, the present disclosure provides deuterated compounds of formula (I),

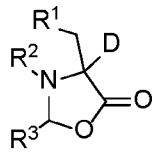


(I),

or a salt thereof, wherein R^1, R^2, and R^3 are as defined herein. Deuterated compounds of formula (I) may be used to prepare various deuterated amino acids and their derivatives.

[0055] In the following, various embodiments of the compounds of formula (I) are disclosed. The first embodiment is denoted E1, the second embodiment is denoted E2 and so forth.

[0056] E1. A deuterated compound of formula (I), or a salt thereof,



(I),

wherein:

R^1 is G^1, C_{1-10}alkyl, $–L^1–R^Y$, or $–G^1\text{-}L^1–R^Y$;

R^2 is an amine protecting group, hydrogen, or C_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{1-4}haloalkyl;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, $–OC_{1-6}$alkyl, $–OG^{1a}$, $–OC_{1-4}$haloalkyl, –SH, $–SC_{1-6}$alkyl, $–SG^{1a}$, $–SC_{1-4}$haloalkyl, $–NH_2$, $–NHC_{1-4}$alkyl, $–NHG^{1a}$, $–N(C_{1-4}\text{alkyl})_2$, $–C(O)C_{1-4}$alkyl, $–C(O)G^{1a}$, $–C(O)OC_{1-4}$alkyl, $–C(O)OG^{1a}$, $–C(O)NH_2$, $–C(O)NHG^{1a}$, $–C(O)NHC_{1-4}$alkyl, $–C(O)N(C_{1-4}\text{alkyl})_2$, $–SO_2C_{1-4}$alkyl, $–SO_2G^{1a}$,

$-SO_2NH_2$, $-SO_2NHC_{1-4}alkyl$, $-SO_2N(C_{1-4}alkyl)_2$, $-C_{1-4}alkylene-OH$, $-C_{1-4}alkylene-OC_{1-4}alkyl$, $-C_{1-4}alkylene-NH_2$, $-C_{1-4}alkylene-NHC_{1-4}alkyl$, $-C_{1-4}alkylene-N(C_{1-4}alkyl)_2$, $-O-C_{1-4}alkylene-OH$, $-O-C_{1-4}alkylene-OC_{1-4}alkyl$, $-O-C_{1-4}alkylene-NH_2$, $-O-C_{1-4}alkylene-NHC_{1-4}alkyl$, $-O-C_{1-4}alkylene-N(C_{1-4}alkyl)_2$, and $C_{1-3}alkylene-G^{1a}$, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, $C_{3-10}carbocyclyl$, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-2}haloalkyl$, halogen, cyano, $-OH$, $-OC_{1-4}alkyl$, $-OC_{1-2}haloalkyl$, $-SH$, $-SC_{1-4}alkyl$, $-SC_{1-2}haloalkyl$, $-NH_2$, $-NHC_{1-4}alkyl$, $-N(C_{1-4}alkyl)_2$, $-C(O)C_{1-4}alkyl$, $-C(O)OC_{1-4}alkyl$,$-C(O)NH_2$, $-C(O)NHC_{1-4}alkyl$, $-C(O)N(C_{1-4}alkyl)_2$, $-SO_2C_{1-4}alkyl$, $-SO_2NH_2$, $-SO_2NHC_{1-4}alkyl$, and $-SO_2N(C_{1-4}alkyl)_2$;

L^1, at each occurrence, is a $C_{1-10}alkylene$, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^X)-$, or $-N(R^X)-$, wherein 2 methylene groups replaced with $-O-$, $-S-$, $-SO-$, $-C(O)O-$, $-C(O)N(R^X)-$, $-SO_2-$, or $-N(R^X)-$ are separated by two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with $-Cy^1-$;

Cy^1 is phenylene, $C_{3-6}cycloalkylene$, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-2}haloalkyl$, and halogen;

R^X is hydrogen, $C_{1-4}alkyl$, $C_{3-4}cycloalkyl$, or $-C_{1-3}alkylene-C_{3-4}cycloalkyl$;

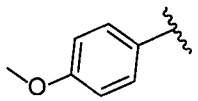
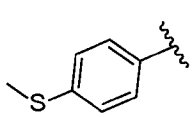
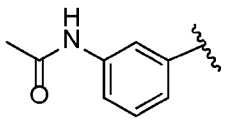
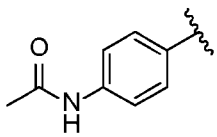
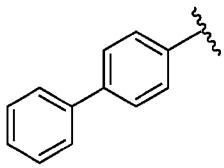
R^Y, at each occurrence, is $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $-OC_{1-4}alkyl$, $-OC_{1-4}haloalkyl$, $-OH$, G^Y, $-OG^Y$, cyano, $-SH$, $-SC_{1-4}alkyl$, $-SC_{1-4}haloalkyl$, $-SG^1$, $-NH_2$, $-NHC_{1-4}alkyl$, $-NHG^Y$, $-N(C_{1-4}alkyl)_2$, $-NHC(O)C_{1-4}alkyl$, $-NHC(O)OC_{1-4}alkyl$, $-C(O)C_{1-4}alkyl$, $-C(O)G^Y$, $-C(O)OG^Y$, $-C(O)OC_{1-4}alkyl$, $-C(O)NH_2$, $-C(O)NHC_{1-4}alkyl$, $-C(O)N(C_{1-4}alkyl)_2$, $-C(O)NHG^Y$, $-C(O)N(G^Y)_2$, $-SO_2C_{1-4}alkyl$, $-SO_2G^Y$, $-SO_2NH_2$, $-SO_2NHC_{1-4}alkyl$, or $-SO_2N(C_{1-4}alkyl)_2$; and

G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –SO_2N(C_{1-4}alkyl)$_2$.

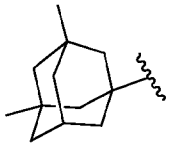
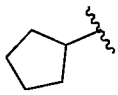
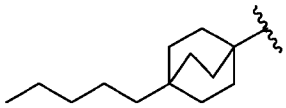
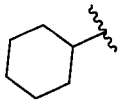
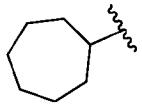
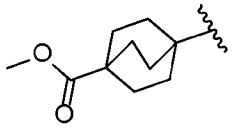
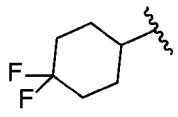
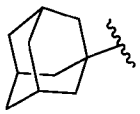
[0057] E2. The deuterated compound of E1, or a salt thereof, wherein R^1 is G^1.

[0058] E3. The deuterated compound of E2, or a salt thereof, wherein G^1 is the optionally substituted 6- to 12-membered aryl.

[0059] E4. The deuterated compound of E3, or a salt thereof, wherein the optionally substituted 6- to 12-membered aryl is optionally substituted phenyl.

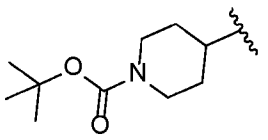
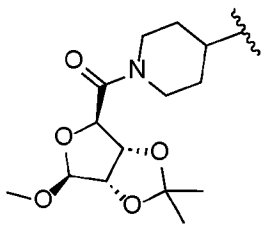
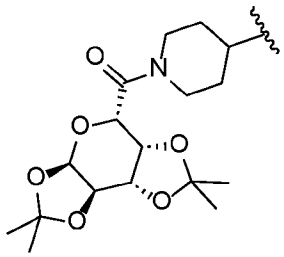
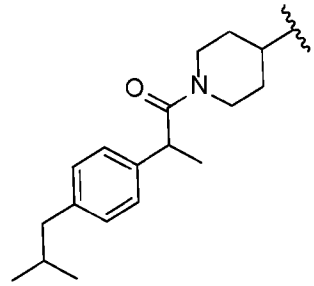
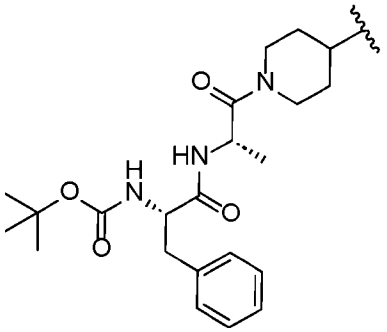
[0060] E5. The deuterated compound of E4, or a salt thereof, wherein G^1 is  ,  ,  ,  , or  .

[0061] E6. The deuterated compound of E2, or a salt thereof, wherein G^1 is the optionally substituted C_{3-10}carbocyclyl.

[0062] E7. The deuterated compound of E6, or a salt thereof, wherein G^1 is  ,  ,  ,  ,  ,  ,  , or  .

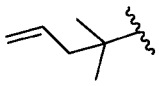
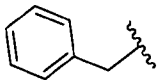
[0063] E8. The deuterated compound of E2, or a salt thereof, wherein G^1 is the optionally substituted 4- to 12-membered heterocyclyl.

[0064] E9. The deuterated compound of E8, or a salt thereof, wherein the optionally substituted 4- to 12-membered heterocyclyl is optionally substituted piperidinyl.

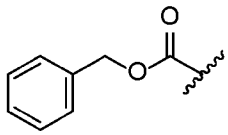
[0065] E10. The deuterated compound of E9, or a salt thereof, wherein G^1 is  ,  ,  ,  , or  .

[0066] E11. The deuterated compound of E1, or a salt thereof, wherein R^1 is $C_{1\text{-}10}$alkyl or $-L^1-R^Y$.

[0067] E12. The deuterated compound of E11, or a salt thereof, wherein R^1 is  or  .

[0068] E13. The deuterated compound of E11, or a salt thereof, wherein R^1 is  or  .

[0069] E14. The deuterated compound of any one of E1-E13, or a salt thereof, wherein R^2 is the amine protecting group.

[0070] E15. The deuterated compound of E14, or a salt thereof, wherein the amine protecting group is  (Cbz).

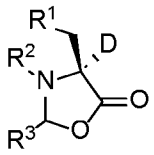
[0071] E16. The deuterated compound of any one of E1-E15, or a salt thereof, wherein R^2 is $C_{1\text{-}6}$alkyl.

[0072] E17. The deuterated compound of E16, or a salt thereof, wherein R^2 is $-CH_3$.

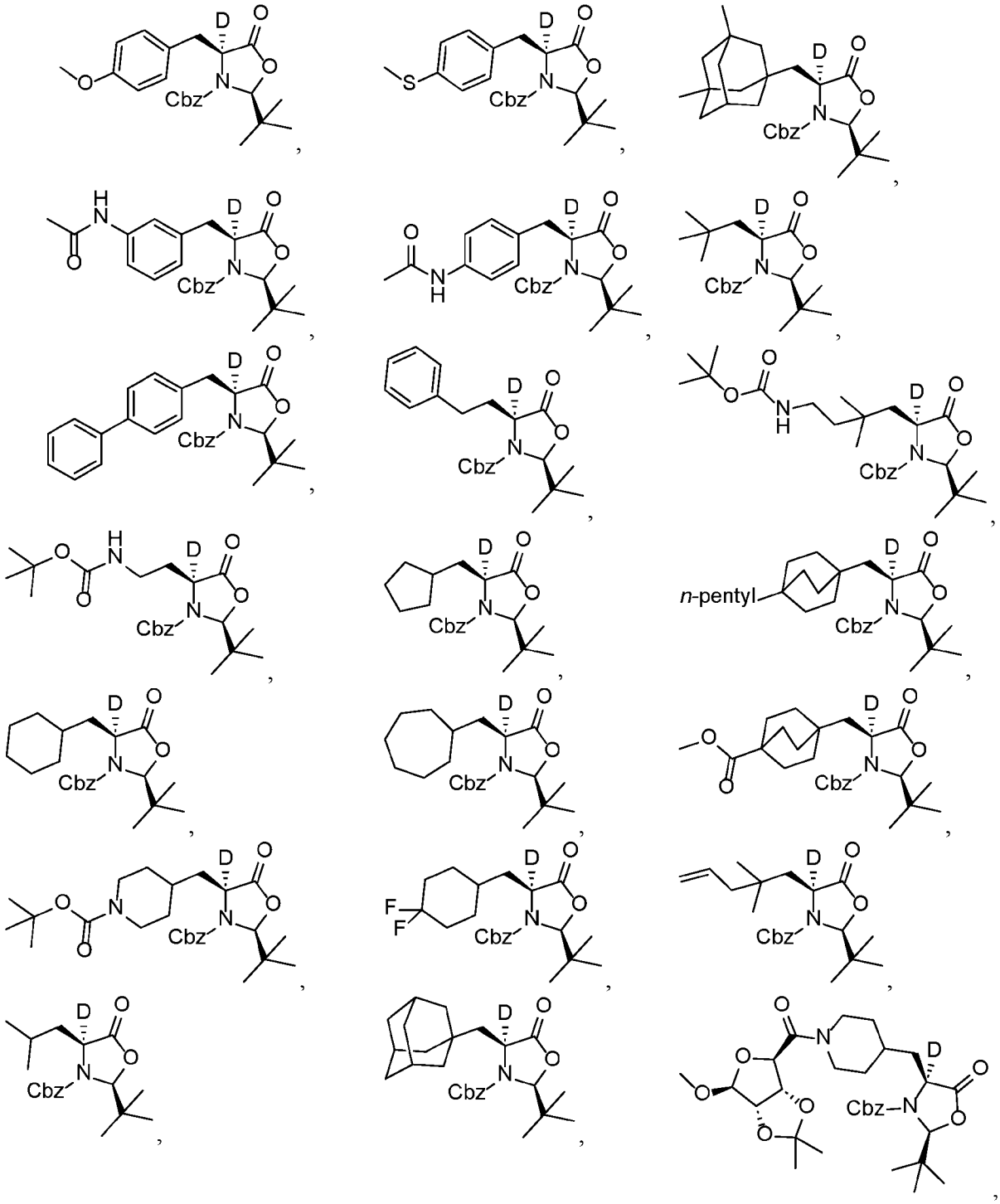
[0073] E18. The deuterated compound of E17, or a salt thereof, wherein each hydrogen in the $-CH_3$ is deuterium.

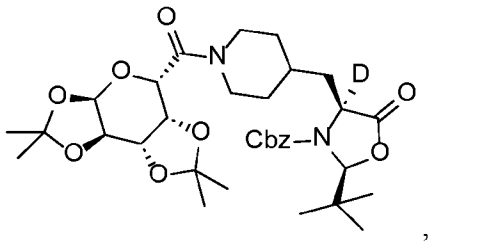
[0074] E19. The deuterated compound of any one of E1-E18, or a salt thereof, wherein R^3 is $C_{1\text{-}6}$alkyl.

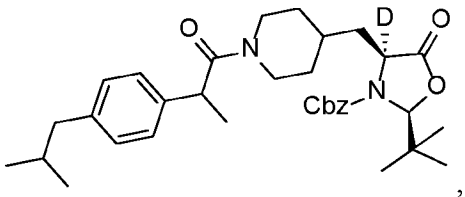
[0075] E20. The deuterated compound of E19, or a salt thereof, wherein R^3 is  .

[0076] E21. The deuterated compound of any one of E1-E20, or a salt thereof, wherein the compound of formula (I) is a compound of formula:  .

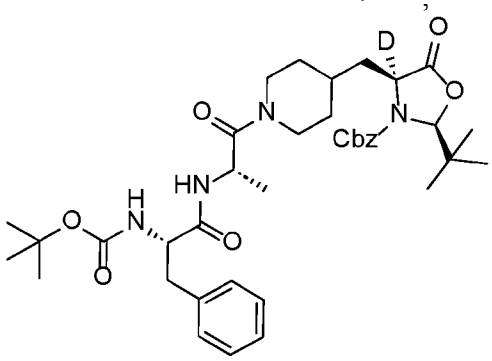
[0077] E22. The deuterated compound of any one of E1-E21, or a salt thereof, wherein the compound of formula (I) is







, or



[0078] E23. The deuterated compound of any one of E1-E22, or a salt thereof, wherein that compound has at least 50% deuterium incorporation at each deuterium label.

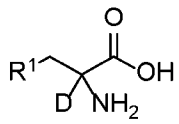
[0079] E24. The deuterated compound of any one of E1-E22, or a salt thereof, wherein that compound has at least 75% deuterium incorporation at each deuterium label.

[0080] E25. The deuterated compound of any one of E1-E22, or a salt thereof, wherein that compound has at least 90% deuterium incorporation at each deuterium label.

[0081] E26. The deuterated compound of any one of E1-E22, or a salt thereof, wherein that compound has at least 95% deuterium incorporation at each deuterium label.

B. Deuterated Compounds of Formula (I-AA)

[0082] In another aspect, the present disclosure provides deuterated compounds of formula (I-AA), or a salt thereof,

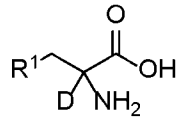


(I-AA),

wherein R^1 is as defined herein. Deuterated compounds of formula (I-AA) may be a deuterated amino acid or a derivative thereof.

[0083] In the following, various embodiments of the compounds of formula (I-AA) are disclosed. The first embodiment is denoted E1, the second embodiment is denoted E2 and so forth.

[0084] E1. A deuterated compound of formula (I-AA), or a salt thereof,



(I-AA),

wherein:

R^1 is G^1, C_{1-10}alkyl, $–L^1–R^Y$, or $–G^1\text{-}L^1–R^Y$;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, $C_{3–10}$carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, $–OC_{1-6}$alkyl, $–OG^{1a}$, $–OC_{1-4}$haloalkyl, –SH, $–SC_{1-6}$alkyl, $–SG^{1a}$, $–SC_{1-4}$haloalkyl, $–NH_2$, $–NHC_{1-4}$alkyl, $–NHG^{1a}$, $–N(C_{1-4}alkyl)_2$, $–C(O)C_{1-4}$alkyl, $–C(O)G^{1a}$, $–C(O)OC_{1-4}$alkyl, $–C(O)OG^{1a}$, $–C(O)NH_2$, $–C(O)NHG^{1a}$, $–C(O)NHC_{1-4}$alkyl, $–C(O)N(C_{1-4}alkyl)_2$, $–SO_2C_{1-4}$alkyl, $–SO_2G^{1a}$, $–SO_2NH_2$, $–SO_2NHC_{1-4}$alkyl, $–SO_2N(C_{1-4}alkyl)_2$, $–C_{1-4}$alkylene–OH, $–C_{1-4}$alkylene–OC_{1-4}alkyl, $–C_{1-4}$alkylene–NH_2, $–C_{1-4}$alkylene–NHC_{1-4}alkyl, $–C_{1-4}$alkylene–$N(C_{1-4}alkyl)_2$, –O–C_{1-4}alkylene–OH, –O–C_{1-4}alkylene–OC_{1-4}alkyl, –O–C_{1-4}alkylene–NH_2, –O–C_{1-4}alkylene–NHC_{1-4}alkyl, –O–C_{1-4}alkylene–$N(C_{1-4}alkyl)_2$, and C_{1-3}alkylene–G^{1a}, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, $C_{3–10}$carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, $–OC_{1-4}$alkyl, $–OC_{1-2}$haloalkyl, –SH, $–SC_{1-4}$alkyl, $–SC_{1-2}$haloalkyl, $–NH_2$, $–NHC_{1-4}$alkyl, $–N(C_{1-4}alkyl)_2$, $–C(O)C_{1-4}$alkyl, $–C(O)OC_{1-4}$alkyl,$–C(O)NH_2$, $–C(O)NHC_{1-4}$alkyl, $–C(O)N(C_{1-4}alkyl)_2$, $–SO_2C_{1-4}$alkyl, $–SO_2NH_2$, $–SO_2NHC_{1-4}$alkyl, and $–SO_2N(C_{1-4}alkyl)_2$;

L^1, at each occurrence, is a C_{1-10}alkylene, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with –O–, –S–, –SO–, $–SO_2–$, –C(O)–, –C(O)O–, $–C(O)N(R^X)–$, or $–N(R^X)–$, wherein 2 methylene groups replaced with –O–, –S–, –SO–, –C(O)O–, $–C(O)N(R^X)–$, $–SO_2–$, or $–N(R^X)–$ are separated by

two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with $-Cy^1-$;

Cy^1 is phenylene, C_{3-6}cycloalkylene, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, and halogen;

R^X is hydrogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, or $-C_{1-3}$alkylene–C_{3-4}cycloalkyl;

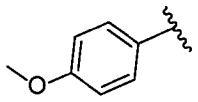
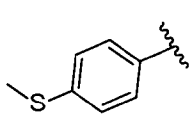
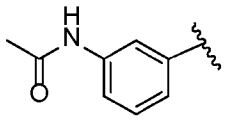
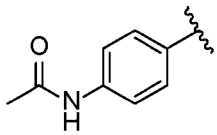
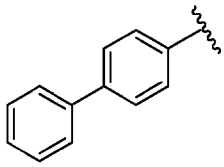
R^Y, at each occurrence, is C_{1-4}alkyl, C_{2-4}alkenyl, $-OC_{1-4}$alkyl, $-OC_{1-4}$haloalkyl, –OH, G^Y, $-OG^Y$, cyano, –SH, $-SC_{1-4}$alkyl, $-SC_{1-4}$haloalkyl, $-SG^1$, $-NH_2$, $-NHC_{1-4}$alkyl, $-NHG^Y$, $-N(C_{1-4}alkyl)_2$, $-NHC(O)C_{1-4}$alkyl, $-NHC(O)OC_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)G^Y$, $-C(O)OG^Y$, $-C(O)OC_{1-4}$alkyl, $-C(O)NH_2$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-C(O)NHG^Y$, $-C(O)N(G^Y)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2G^Y$, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, or $-SO_2N(C_{1-4}alkyl)_2$; and

G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, $-OC_{1-4}$alkyl, $-OC_{1-2}$haloalkyl, –SH, $-SC_{1-4}$alkyl, $-SC_{1-2}$haloalkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-C(O)C_{1-4}$alkyl, $-C(O)OC_{1-4}$alkyl,$-C(O)NH_2$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, and $-SO_2N(C_{1-4}alkyl)_2$.

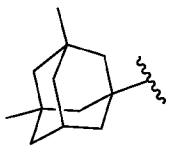
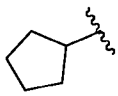
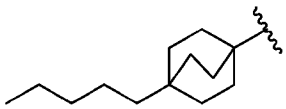
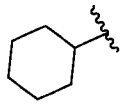
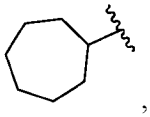
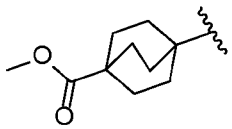
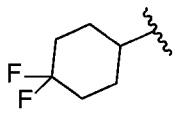
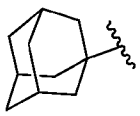
[0085] E2. The deuterated compound of E1, or a salt thereof, wherein R^1 is G^1.

[0086] E3. The deuterated compound of E2, or a salt thereof, wherein G^1 is the optionally substituted 6- to 12-membered aryl.

[0087] E4. The deuterated compound of E3, or a salt thereof, wherein the optionally substituted 6- to 12-membered aryl is optionally substituted phenyl.

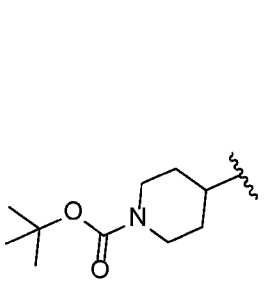
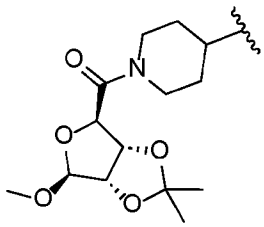
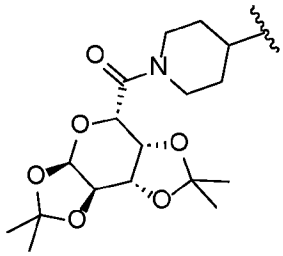
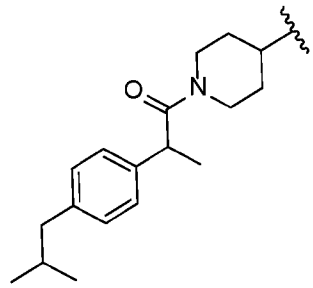
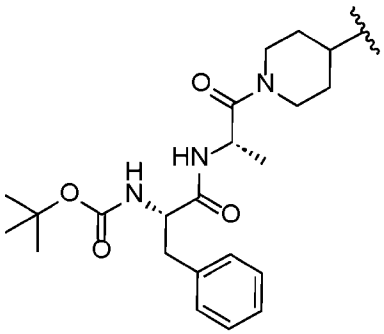
[0088] E5. The deuterated compound of E4, or a salt thereof, wherein G^1 is  ,  ,  ,  , or  .

[0089] E6. The deuterated compound of E2, or a salt thereof, wherein G^1 is the optionally substituted C_{3-10}carbocyclyl.

[0090] E7. The deuterated compound of E6, or a salt thereof, wherein G^1 is  ,  ,  ,  ,  ,  ,  , or  .

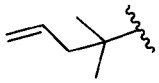
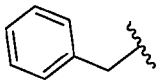
[0091] E8. The deuterated compound of E2, or a salt thereof, wherein G^1 is the optionally substituted 4- to 12-membered heterocyclyl.

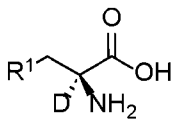
[0092] E9. The deuterated compound of E8, or a salt thereof, wherein the optionally substituted 4- to 12-membered heterocyclyl is optionally substituted piperidinyl.

[0093] E10. The deuterated compound of E9, or a salt thereof, wherein G^1 is  ,  ,  ,  , or  .

[0094] E11. The deuterated compound of E1, or a salt thereof, wherein R^1 is $C_{1\text{-}10}$alkyl or $-L^1-R^Y$.

[0095] E12. The deuterated compound of E11, or a salt thereof, wherein R^1 is  or  .

[0096] E13. The deuterated compound of E11, or a salt thereof, wherein R^1 is  or  .

[0097] E14. The deuterated compound of any one of E1-E13, or a salt thereof, wherein the compound of formula (I) is a compound of formula:  .

[0098] E15. The deuterated compound of any one of E1-E14, or a salt thereof, wherein that compound has at least 50% deuterium incorporation at each deuterium label.

[0099] E16. The deuterated compound of any one of E1-E14, or a salt thereof, wherein that compound has at least 75% deuterium incorporation at each deuterium label.

[00100] E17. The deuterated compound of any one of E1-E14, or a salt thereof, wherein that compound has at least 90% deuterium incorporation at each deuterium label.

[00101] E18. The deuterated compound of any one of E1-E14, or a salt thereof, wherein that compound has at least 95% deuterium incorporation at each deuterium label.

[00102] Compounds may exist as a stereoisomer wherein asymmetric or chiral centers are present. The stereoisomer is "*R*" or "*S*" depending on the configuration of substituents around the chiral carbon atom. The terms "*R*" and "*S*" used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in Pure Appl. Chem., 1976, 45: 13-30. The disclosure contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of this invention. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. In the compounds of formulae (I) and (II), when no specific configuration is indicated at a stereogenic center (e.g., carbon), the compounds include all possible stereoisomers.

[00103] Individual stereoisomers of the compounds may be prepared synthetically from commercially available starting materials, which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, "Vogel's Textbook of Practical Organic Chemistry," 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England, or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns, or (3) fractional recrystallization methods.

[00104] The compound may possess tautomeric forms, as well as geometric isomers, and that these also constitute an aspect of the invention.

[00105] In the compounds of formulae (I), (II), and any subformulas, any "hydrogen" or "H," whether explicitly recited or implicit in the structure, encompasses hydrogen isotopes ^{1}H (protium) and ^{2}H (deuterium).

[00106] The present disclosure also includes isotopically-labeled compounds (e.g., deuterium labeled), where an atom in the isotopically-labeled compound is specified as a particular isotope

of the atom. Examples of isotopes suitable for inclusion in the compounds of the invention are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[00107] Isotopically-enriched forms of compounds of formulae (I), (II), or any subformulas, may generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using an appropriate isotopically-enriched reagent in place of a non-isotopically-enriched reagent. The extent of isotopic enrichment can be characterized as a percent incorporation of a particular isotope at an isotopically-labeled atom (e.g., % deuterium incorporation at a deuterium label).

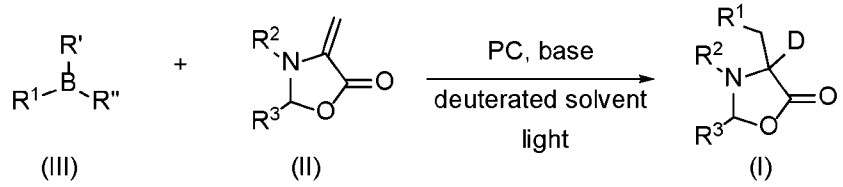
III. Exemplary Synthetic Methods

[00108] Deuterated compounds of formula (I) and formula (I-AA) may be prepared by exemplary synthetic processes depicted in the following schemes, where R', R", R^1, R^2, and R^3 are defined as described herein.

[00109] Abbreviations which have been used in the descriptions and schemes that follow are:
W is watts;
LED is light emitting diode; and
PC is photocatalyst.

[00110] General Scheme 1, below, illustrates the method for preparing deuterated compounds of formula (I), described herein.

General Scheme 1.



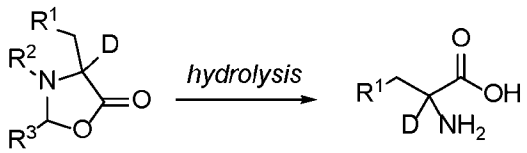
(III) (II) (I)

[00111] As shown in General Scheme 1 above, deuterated compounds of formula (I) may be prepared by mixing a compound of formula (III), with a compound of formula (II), a photocatalyst, a base (e.g., a Lewis base), and a deuterated solvent (e.g., D_2O) to form a reaction mixture. The

reaction mixture may then be exposed to light (e.g., a blue LED light), thereby producing the deuterated compound of formula (I).

[00112] General Scheme 2, below, illustrates the method for preparing deuterated compounds of formula (I-AA), described herein.

General Scheme 2.



(I) (I-AA)

[00113] As shown in General Scheme 2 above, deuterated compounds of formula (I-AA) may be prepared by subjecting a deuterated compound of formula (I) to suitable hydrolysis conditions (e.g., acid and heating), thereby hydrolyzing the deuterated compound of formula (I) and providing a deuterated compound of formula (I-AA).

A. Exemplary Reaction Mixtures

1. Molar Ratios of Compound of Formula (II) to Formula (III)

[00114] For exemplary mixtures, in various instances, the molar ratio of the compound of formula (II) to the compound of formula (III) may be 1.0 to 3.0. In some instances, the molar ratio of the compound of formula (II) to the compound of formula (III) may be 1.1 to 2.9; 1.2 to 2.8; 1.3 to 2.7; 1.4 to 2.6; 1.5 to 2.5; 1.6 to 2.4; 1.7 to 2.3; 1.8 to 2.2; or 1.9 to 2.1. In some instances, the molar ratio of the compound of formula (II) to the compound of formula (III) may be no less than 1.0; no less than 1.1; no less than 1.2; no less than 1.3; no less than 1.4; no less than 1.5; no less 1.6; no less 1.7; no less 1.8; no less than 1.9; no less than 2.0; no less than 2.1; no less than 2.2; no less than 2.3; no less than 2.4; no less than 2.5; no less than 2.6; no less 2.7; no less than 2.8; or no less than 2.9. In some instances, the molar ratio of the compound of formula (II) to the compound of formula (III) may be no greater than 3.0; no greater than 2.9; no greater than 2.8; no greater than 2.7; no greater than 2.6; no greater than 2.5; no greater than 2.4; no greater than 2.3; no greater than 2.2; no greater than 2.1; no greater than 2.0; no greater than 1.9; no greater than

1.8; no greater than 1.7; no greater than 1.6; no greater than 1.5; no greater than 1.4; no greater than 1.3; no greater than 1.2; or no greater than 1.1.

2. Solvents

[00115] In various instances, the solvent of the mixture may be a deuterated solvent. The deuterated solvent may comprise deuterated water (D_2O) and/or deuterated methanol (MeOD). In various instances, the solvent of the mixture may further comprise a second solvent. The second solvent may be an organic solvent. In some instances, the organic solvent may be a polar aprotic solvent. Exemplary polar aprotic solvents include, without limitation, acetone, acetonitrile (MeCN), tetrahydrofuran (THF), dichloromethane (DCM), 1,4-dioxane, dimethylsulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and combinations thereof.

3. Compound of Formula (II) Concentrations

[00116] In various instances, the compound of formula (II) may be present in the mixture at a concentration of 0.05 M to 0.2 M. In some instances, the compound of formula (II) may be present in the mixture at a concentration of 0.06 M to 0.19 M; 0.07 M to 0.18 M; 0.08 M to 0.17 M; 0.09 M to 0.16 M; 0.1 M to 0.15 M; 0.11 M to 0.14 M; or 0.12 to 0.13 M. In some instances, the compound of formula (II) may be present in the mixture at a concentration of no greater than 0.2 M; no greater than 0.18 M; no greater than 0.15 M; no greater than 0.13 M; no greater than 0.10 M; or no greater than 0.07 M. In some instances, the compound of formula (II) may be present in the mixture at a concentration of no less than 0.05 M; no less than 0.07 M; no less than 0.1 M; no less than 0.13 M; no less than 0.15 M; or no less than 0.17 M.

4. Photocatalysts

[00117] In various instances, the mixture may comprise a catalyst. The catalyst may be a photocatalyst. As used herein, the term "photocatalyst" means a catalyst that, upon irradiation with ultraviolet (UV)- or visible light generates electron-hole pairs that generate free radicals). Exemplary photocatalysts include any catalyst operable to participate in deuteration mechanisms described herein may be used in the reaction mixture.

[00118] In various instances the photocatalyst may comprise an iridium (Ir)-based photocatalyst and/or a ruthenium (Ru)-based photocatalyst. In some instances, the iridium (Ir)-based photocatalyst may include one or more iridium (Ir) complexes. In some instances, the ruthenium (Ru)-based photocatalyst may include one or more ruthenium (Ru) complexes. In some instances,

the photocatalyst may comprise iridium and/or ruthenium complexes. Suitable iridium complexes may include, without limitation $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$, $Ir(dF(CF_3)ppy)_2(4,4'\text{-dcbpy})$ and $Ir(ppy)_2(dtbbpy)^+$. Homoleptic iridium complexes, such as $Ir(dFppy)_3$, may also be used as photocatalyst. In some instances, the photocatalyst may be [4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate ($Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$) or tris(2,2'-(*p*-$CF_3$)bipyridine)ruthenium(II)tetrafluoroborate ($Ru(bpy)_3(BF_4)_2$).

[00119] In other instances, the photocatalyst may comprise 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), 9-Mesityl-10-methylacridinium Perchlorate ($Mes\text{-}Acr\text{-}Me^+ \cdot ClO_4^-$), 6-Cl-isatin, isatin, Eosin Y, Rose Bengal, or combinations thereof.

[00120] In various instances, exemplary reaction mixtures may comprise the photocatalyst at 0.1 mole % (mol%) to 5 mol%. In various instances, exemplary reaction mixtures may comprise the photocatalyst at 0.25 mol% to 4.5 mol%; 0.5 mol% to 4 mol%; 0.75 mol% to 3.5 mol%; 1 mol% to 3 mol%; 1.5 mol% to 2.5 mol%; or 1.75 mol% to 2.25 mol%. In various instances, exemplary reaction mixtures may comprise the photocatalyst at no greater than 5 mol%; no greater than 4.5 mol%; no greater than 4 mol%; no greater than 3.5 mol%; no greater than 3 mol%; no greater than 2.5 mol%; no greater than 2 mol%; no greater than 1.5 mol%; no greater than 1 mol%; no greater than 0.5 mol%; or no greater than 0.25 mol%. In various instances, exemplary reaction mixtures may comprise the photocatalyst at no less than 0.1 mol%; no less than 0.25 mol%; no less than 0.5 mol%; no less than 1 mol%; no less than 1.5 mol%; no less than 2 mol%; no less than 2.5 mol%; no less than 3 mol%; or no less than 3.5 mol%.

5. Bases

[00121] In various instances, exemplary reaction mixtures may further comprise a base. Exemplary bases include, without limitation, organic bases, inorganic bases, and combinations thereof. In some instances, the base may comprise an electron-accepting cation (e.g., sodium (Na^+), lithium (Li^+), and/or potassium (K^+)) and an electron-donating anion (e.g., acetate (OAc^-), carbonate (CO_3^{-2})). Example bases that may be present in the mixture include, without limitation,

sodium acetate (NaOAc), potassium acetate (KOAc), lithium acetate (LiOAc), and combinations thereof.

[00122] In various instances, the base may be a Lewis base. As used herein, the term "Lewis base" means a base capable a pair of non-bonding electrons, i.e., an electron pair donor. In various instances, the Lewis base may be quinuclidinol or 1,4-diazabicyclo[2.2. 2]octane (DABCO).

[00123] In various instances, the molar ratio of base to compound of formula (II) may be 0.1 to 3.0. In various instances, the molar ratio of base to compound of formula (II) may be 0.2 to 2.8; 0.3 to 2.7; 0.4 to 2.6; 0.5 to 2.5; 0.6 to 2.4; 0.7 to 2.3; 0.8 to 2.2; or 0.9 to 2.1. In various instances, the molar ratio of base to compound of formula (II) may be no greater than 3.0; no greater than 2.8; no greater than 2.6; no greater than 2.5; no greater than 2.2; no greater than 2.0; no greater than 1.8; no greater than 1.5; no greater than 1.2; no greater than 1.0; no greater than 0.8; no greater than 0.5; or no greater than 0.2. In various instances, the molar ratio of base to compound of formula (II) may be no less than 0.1; no less than 0.3; no less than 0.5; no less than 0.8; no less than 1.0; no less than 1.2; no less than 1.5; no less than 1.7; no less than 2.0; no less than 2.2; no less than 2.5; no less than 2.7; or no less than 2.8.

B. Exemplary Reaction Conditions

1. Light Source

[00124] In some instances, the light may be provided from one or more light emitting diode (LED) light sources. Exemplary LED light sources include, without limitation, white LED, purple LED, blue LED, and combinations thereof. In various instances, the light may be provided from one or more blue LED light sources. In some instances, the blue LED light source is a 40 W Kessil Blue LED.

2. Atmosphere

[00125] In various instances, exposing the mixture to light may occur in the absence of oxygen (O_2). For instance, the mixture to light may occur under argon (Ar) atmosphere or nitrogen (N_2) atmosphere.

3. Time Period

[00126] In various instances, exposing the mixture to light may occur for a time period of 12 to 48 hours. In some instances, exposing the mixture to light may occur for a time period of 14 to 46

hours; 15 to 45 hours; 18 to 42 hours; 20 to 40 hours; 22 to 38 hours; 23 to 37 hours; 24 to 36 hours; 25 to 35 hours; 26 to 34 hours; 27 to 33 hours; or 28 to 32 hours. In some instances, exposing the mixture to light may occur for a time period of no greater than 48 hours; no greater than 45 hours; no greater than 42 hours; no greater than 40 hours; no greater than 38 hours; no greater than 36 hours; no greater than 32 hours; no greater than 30 hours; no greater than 28 hours; no greater than 26 hours; no greater than 24 hours; no greater than 20 hours; no greater than 18 hours; no greater than 16 hours; or no greater than 14 hours. In some instances, exposing the mixture to light may occur for a time period of no less than 12 hours; no less than 14 hours; no less than 16 hours; no less than 18 hours; no less than 20 hours; no less than 22 hours; no less than 24 hours; no less than 26 hours; no less than 28 hours; no less than 30 hours; no less than 34 hours; no less than 36 hours; no less than 40 hours; no less than 44 hours; or no less than 46 hours.

4. Temperature

[00127] In various instances, during light exposure, the mixture may be maintained at a temperature of 22 °C to 42 °C. In some instances, while being exposed to light, the mixture may be maintained at a temperature of 23 °C to 41 °C; 24 °C to 40 °C; 25 °C to 39 °C; 26 °C to 38 °C; 26 °C to 38 °C; 27 °C to 37 °C; 28 °C to 36 °C; 29 °C to 35 °C; 30 °C to 34 °C; or 31 °C to 32 °C. In some instances, during light exposure, the mixture may be maintained at a temperature of no greater than 42 °C; no greater than 40 °C; no greater than 38 °C; no greater than 36 °C; no greater than 34 °C; no greater than 32 °C; no greater than 30 °C; no greater than 28 °C; no greater than 26 °C; or no greater than 24 °C. In some instances, during light exposure, the mixture may be maintained at a temperature of no less than 22 °C; no less than 24 °C; no less than 26 °C; no less than 28 °C; no less than 30 °C; no less than 32 °C; no less than 34 °C; no less than 36 °C; no less than 38 °C; or no less than 40 °C.

[00128] The compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989),

by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

[00129] A disclosed compound may have at least one basic nitrogen whereby the compound can be treated with an acid to form a desired salt. For example, a compound may be reacted with an acid at or above room temperature to provide the desired salt, which is deposited, and collected by filtration after cooling. Examples of acids suitable for the reaction include, but are not limited to tartaric acid, lactic acid, succinic acid, as well as mandelic, atrolactic, methanesulfonic, ethanesulfonic, toluenesulfonic, naphthalenesulfonic, benzenesulfonic, carbonic, fumaric, maleic, gluconic, acetic, propionic, salicylic, hydrochloric, hydrobromic, phosphoric, sulfuric, citric, hydroxybutyric, camphorsulfonic, malic, phenylacetic, aspartic, or glutamic acid, and the like.

[00130] Optimum reaction conditions and reaction times for each individual step can vary depending on the reactants employed and substituents present in the reactants used. Specific procedures are provided in the Examples section. Reactions can be worked up in the conventional manner, e.g., by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration, and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature. Starting materials, if not commercially available, can be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above-described schemes or the procedures described in the synthetic examples section.

[00131] Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled Protective Groups in Organic Synthesis (4^{th} ed.), John Wiley & Sons, NY (2006), which is incorporated herein by reference in its entirety.

Synthesis of the compounds of the invention can be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

[00132] When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization, or enzymatic resolution).

[00133] Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

[00134] It can be appreciated that the synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the invention as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

IV. Experimental Examples

[00135] Without limiting the scope of the instant disclosure, various experimental examples of embodiments discussed above were prepared and the results are discussed below.

[00136] Abbreviations that may be used in the examples that follow are:

NaOAc is sodium acetate;

EtOAc is ethyl acetate;

Me is methyl;

Et is ethyl;

Ph is phenyl;

Ac is acetyl;

Bn is benzyl;

MeCN is acetonitrile;

THF is tetrahydrofuran;

D_2O is deuterated water;

DABCO is 1,4-diazabicyclo[2.2. 2]octane;

DMSO is dimethylsulfoxide;

DCM is dichloromethane;

DCC is N,N'-dicyclohexylcarbodiimide;

DMA is dimethylacetamide;

DMF is *N*,*N*-dimethylformamide;

DMAP is 4-dimethylaminopyridine;

CH_3OD is deuterated methanol;

Cbz is benzyloxycarbonyl;

Boc is *tert*-butyloxycarbonyl;

$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ is [4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate;

Mes-Acr-$Me^+ \cdot ClO_4^-$ is 9-Mesityl-10-methylacridinium Perchlorate;

4CzIPN is 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene;

$Ru(bpy)_3(BF_4)_2$ is Tris(2,2'-(*p*-CF_3)bipyridine)ruthenium(II)tetrafluoroborate;

Molar is M;

rt, RT, or r.t. is room temperature;

sat. is saturated;

eq, eq., or equiv is equivalent(s);

wt% or wt.% is weight %;

PC is photocatalyst;

TEA is triethyl amine;

LED is light emitting diode;

TLC is thin layer chromatography;

UV is ultraviolet;

HRMS is high resolution mass spectrometry;

LCMS is liquid chromatography mass spectrometry; and

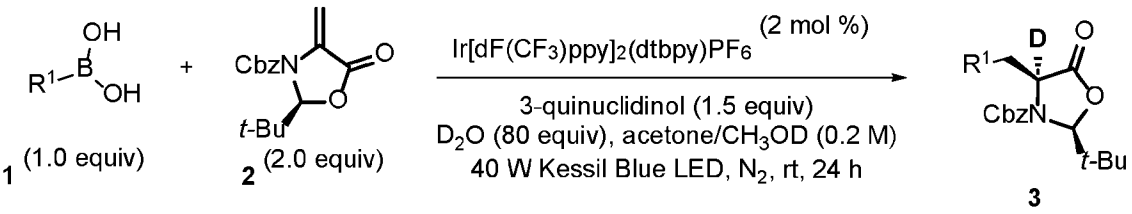
ESI-TOF is electrospray ionization time-of-flight.

1. General Information

[00137] Starting materials **1a-1t** are commercially available reagents, which were purchased from Sigma Aldrich, Matrix Chemical, AK Sci, Alfa Aesar, TCI, Aurora Building Blocks 9, Aurora Fine Chemicals LLC, 4DrugDiscovery LLC, Aquila Pharmatech Product List, Chemieliva Pharmaceutical Product List and Chem Cruz, and used as received unless otherwise noted. Kessil A160WE Controllable LED Aquarium Lights (40w, 440nm) were purchased from Amazon. Except Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with a fluorescence F254 indicator were used for thin-layer chromatography (TLC) analysis. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance 400/500. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) as internal standards. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet), coupling constant in Hertz (Hz) and hydrogen numbers based on integration intensities. ^{13}C NMR chemical shifts are reported in ppm relative to the central peak of $CDCl_3$ (77.16 ppm) as internal standards. High-resolution mass spectrometry was performed in Analytical and Biological Mass Spectrometry Center.

2. General Procedure and Evaluation of Reaction Conditions

2.1 General Procedure:



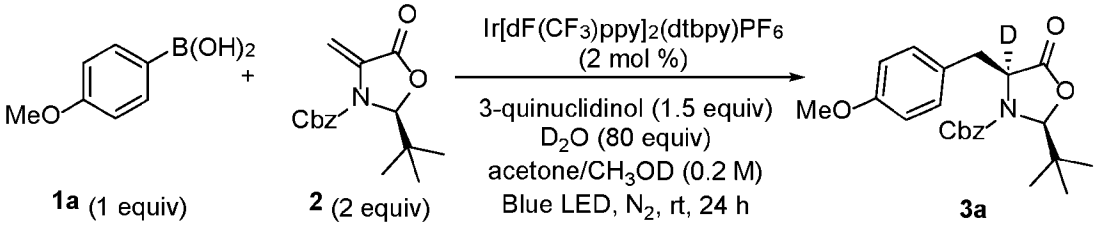
[00138] To an oven-dried 20 mL-Schlenk tube equipped with a stir bar, were added boronic acid **1** (0.2 mmol, 1.0 equiv), and Lewis base (0.3 mmol, 1.5 equiv). Then acetone/CH_3OD (1:1 v/v, 0.2M, 0.5 mL) and 80 equiv. D_2O was added using a syringe. The solution was then stirred at rt for 1 h. After pretreated of **1** and **2**, chiral dehydroalanine (0.4 mmol, 2.0 equiv) and $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2 mol %) dissolved in acetone/CH_3OD (1:1 v/v, 0.2M, 0.5 mL) was added using a syringe. The technique "freeze-pump-thaw" (three times) was applied to the reaction system to remove the oxygen. The solution was then stirred at room temperature under the irradiation of two 40 W Kessil Blue LEDs for 24 h using electronic fan to cool the tube. The

distance between Blue LEDs and solution is 1-2 cm. After completion of the reaction, 2 mL of water was added and extracted by EtOAc. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexane/ethyl acetate.

2.2 Reaction Conditions Evaluation

[00139] The reaction of 4-methoxyphenylboronic acid (**1a**, 1.0 equiv.), (*S*)-methyleneoxazolidinone (**2**, 2.0 equiv), D_2O (80.0 equiv) as the deuterium source and a photocatalyst (PC) irradiated by 40 W Kessil blue LED was probed. Commonly used quinuclidin-3-ol (1.5 equiv) as the Lewis base (LB) in photoredox deboronation was tested in acetone/MeOD (1:1 (v/v)) as the solvent for 24 h. The studies revealed that the reaction efficiency was PC-dependent (**Table 1** entries 1−2 and **Table 2**).

Table 1. Reaction Condition Evaluation

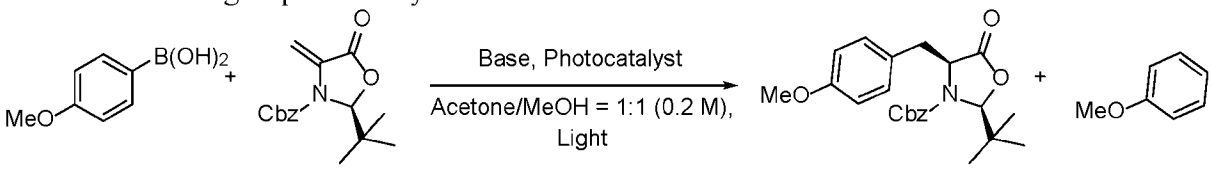


entry	derivation from standard conditions[a]	yield (%)[b], D-content (%)[c], dr[d]
1	none	57%, 95%, >20:1
2	4CzIPN as PC	34%, 95%, >20:1
3	DMF as solvent	20%, 74%, >20:1
4	acetone as solvent	41%, 89%, >20:1
5	0.1M concentration	53%, 95%, >20:1
7	0.5 equiv of **2** used	24%, 95%, >20:1
8	0.2 equiv of base	41%, 96%, >20:1
9	quinuclidine as base	55%, 95%, >20:1
10	DMAP as base	45%, 96%, >20:1
11	Cs_2CO_3 as base	32%, 95%, >20:1
12	without pretreat **1a** and LB	56%, 81%, >20:1
13	no base	<10%, ND[e]

entry	derivation from standard conditions[a]	yield (%)[b], D-content (%)[c], dr[d]
14	no light or no photocatalyst	0

[a] Reaction conditions: unless specified, to a 20 mL-disposable scintillation vial equipped with a stir bar, were added boronic acid **1** (0.2 mmol), and Lewis base (0.3 mmol). Then acetone/CH_3OD (0.5 mL) and D_2O (80 equiv) was added via syringe. The solution was then stirred at rt for 1 h. Compound **2** (0.4 mmol) and photocatalyst (PC, 2 mol %) dissolved in acetone/CH_3OD (0.5 mL) were added to the above solution via syringe. The "freeze-pump-thaw" was run three times to remove oxygen. The solution was then stirred at rt under the irradiation of two 40 W Kessil blue LEDs for 24 h using electronic fan to cool the tube. [b] Yield of isolated products. [c] Determined by 1H NMR. [d] Determined by 1H NMR. [e] ND: not determined.

Table 2. Screening of photocatalyst[a, b]



1 2 3a' 4

Entry	Base	photocatalyst	Time	Yield	Notes
1	1.5 eq Quinuclidinol	Mes-Acr-$Me^+ \cdot ClO_4^-$	24h	45%	40w Blue LED
2	1.5 eq Quinuclidinol	$Ru(bpy)_3(BF_4)_2$	24h	26%	40w Blue LED
3	1.5 eq Quinuclidinol	$Ir(ppy)_2(dtbpy)PF_6$	24h	15%	40w Blue LED
4	1.5 eq Quinuclidinol	Eosin Y	24h	0%	40w Blue LED
5	1.5 eq Quinuclidinol	Rose Begal	24h	0%	40w Blue LED

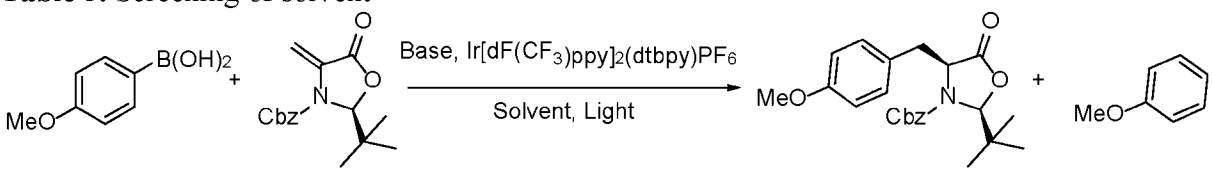
[a]Yield is determined by ^1H NMR using 1,3,5-Trimethoxybenzene as internal standard. [b]**4** is detected by LC-MS.

[00140] Among the PCs probed, $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ delivered the desired product **3a** in 57% yield (**Table 1**, entry 1). There was a noticeable amount of deboronated byproduct formed (**Table 2**). In addition, the reaction delivered the product with 95% D-incorporation and an excellent level of diastereometric ratio (dr, > 20:1).

[00141] Further reaction condition optimization by probing the solvent (**Table 1**, entries 3-4 and **Table 3**), the concentration (**Table 1**, entry 5), ratio between **1a** and **2** (**Table 1**, entry 7), base (**Table 1**, entries 8-11, and **Table 4** and **Table 6**) and deuterium source (**Table 5** and **Table 7**)

revealed the optimized reaction conditions: 1.5 equiv of quinuclidin-3-ol, 2.0 equiv of **2**, 0.2 M of concentration and acetone/MeOD as co-solvent (**Table 1**, entry 1). The control experiments validated that base, light, and photocatalyst were essential for the process (**Table 1**, entries 8−10).

Table 3. Screening of solvent[a,b]

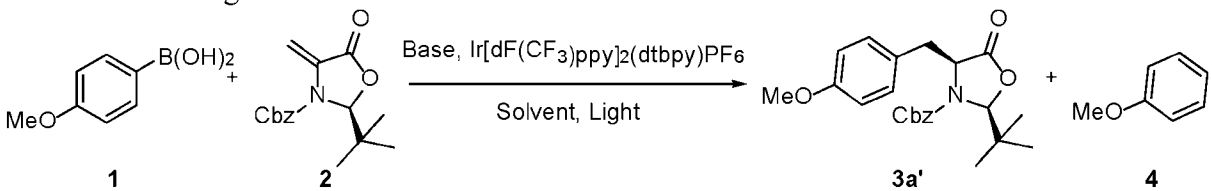


1 2 3a' 4

Entry	Base	Solvent	Time	Yield	Notes
1	1.5 eq Quinuclidinol	THF (0.2 M)	24h	47%	40w Blue LED
2	1.5 eq Quinuclidinol	DMA (0.2 M)	24h	21%	40w Blue LED
3	1.5 eq Quinuclidinol	DMSO (0.2 M)	24h	0%	40w Blue LED
4	1.5 eq Quinuclidinol	MeCN (0.2 M)	24h	17%	40w Blue LED
5	1.5 eq Quinuclidinol	MeOH (0.2 M)	24h	27%	40w Blue LED
6	1.5 eq Quinuclidinol	Acetone/MeOH = 95:5 (0.2 M)	24h	43%	40w Blue LED

[a]Yield is determined by ^{1}H NMR using 1,3,5-Trimethoxybenzene as internal standard. [b]**4** is detected by LC-MS.

Table 4. Screening of base[a,b]



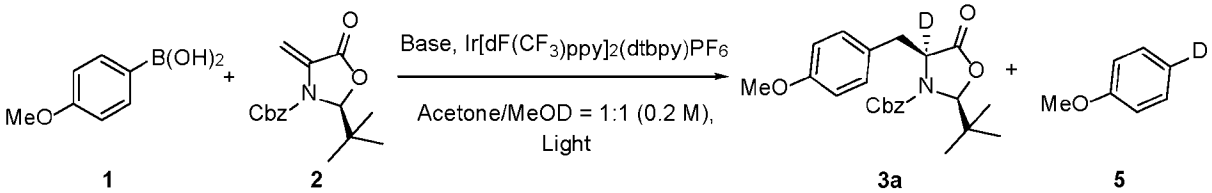
1 2 3a' 4

Entry	Base	Solvent	Time	Yield	Notes
1	1.5 eq NaOAc	Acetone/ MeOH = 1:1 (0.2 M)	24h	21%	40w Blue LED
2	1.5 eq NaOH	Acetone/ MeOH = 1:1 (0.2 M)	24h	30%	40w Blue LED

Entry	Base	Solvent	Time	Yield	Notes
3	1.5 eq K_2CO_3	Acetone/ MeOH = 1:1 (0.2 M)	24h	31%	40w Blue LED
4	1.5 eq DBU	Acetone/MeOH = 1:1 (0.2 M)	24h	17%	40w Blue LED
5	1.5 eq DABCO	Acetone/MeOH = 1:1 (0.2 M)	24h	44%	40w Blue LED
6	1.5 eq TEA	Acetone/MeOH = 1:1 (0.2 M)	24h	<10%	40w Blue LED
7	1.5 eq Pyridine	Acetone/MeOH = 1:1 (0.2 M)	24h	<10%	40w Blue LED

[a]Yield is determined by ^{1}H NMR using 1,3,5-Trimethoxybenzene as internal standard. [b]**4** is detected by LC-MS.

Table 5. Scan with deuterium source[a,b]

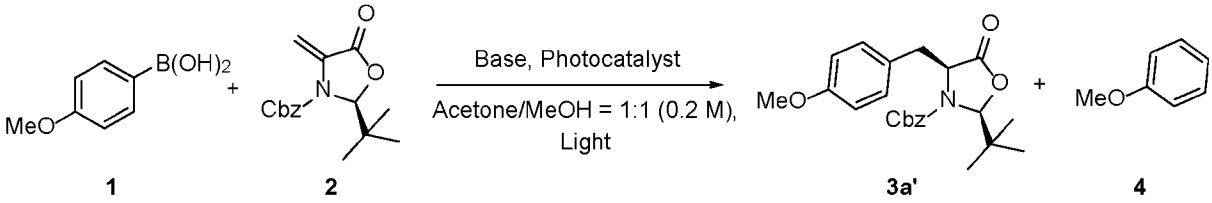


1 2 3a 5

Entry	Base	D source	Time	Yield, D-content	Notes
1	1.5 eq Quinuclidinol	no D_2O	24h	55%, 58%	40w Blue LED
2	1.5 eq Quinuclidinol	20 eq D_2O	24h	56%, 67%	40w Blue LED
3	1.5 eq Quinuclidinol	40 eq D_2O	24h	56%, 74%	40w Blue LED
4	1.5 eq Quinuclidinol	60 eq D_2O	24h	56%, 82%	40w Blue LED
5	1.5 eq Quinuclidinol	100 eq D_2O	24h	56%, 87%	40w Blue LED
6	1.5 eq Quinuclidinol	150 eq D_2O	24h	56%, 90%	40w Blue LED
7	1.5 eq Quinuclidinol	250 eq D_2O	24h	56%, 91%	40w Blue LED

[a]Yield is calculated after isolation. [b]First dissolve Lewis base and boric acid in D source/Acetone/CH_3OD and stir for 1h. **5** is detected by LC-MS.

Table 6. Screening of amount of Lewis Base[a,b]

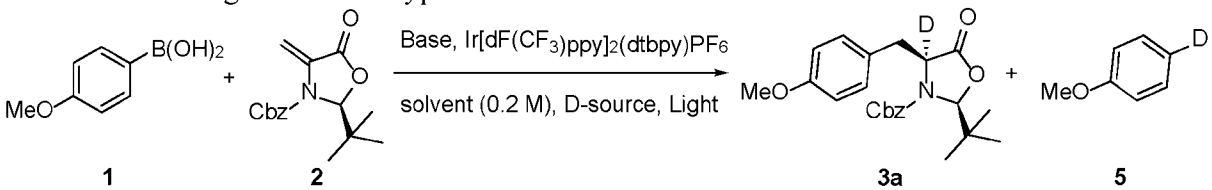


1 2 3a' 4

Entry	Base	Photocatalyst	Time	Yield	Notes
1	0.2 eq Quinuclidinol	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	24h	25%	40w Blue LED
2	0.5 eq Quinuclidinol	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	24h	35%	40w Blue LED
3	1.0 eq Quinuclidinol	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	24h	43%	40w Blue LED
4	1.5 eq Quinuclidinol	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	24h	57%	40w Blue LED
5	2 eq Quinuclidinol	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	24h	55%	40w Blue LED

[a]Yield is determined by ^1H NMR using 1,3,5-Trimethoxybenzene as internal standard. [b]**4** is detected by LC-MS.

Table 7. Screening of different type of methanol[a,b]



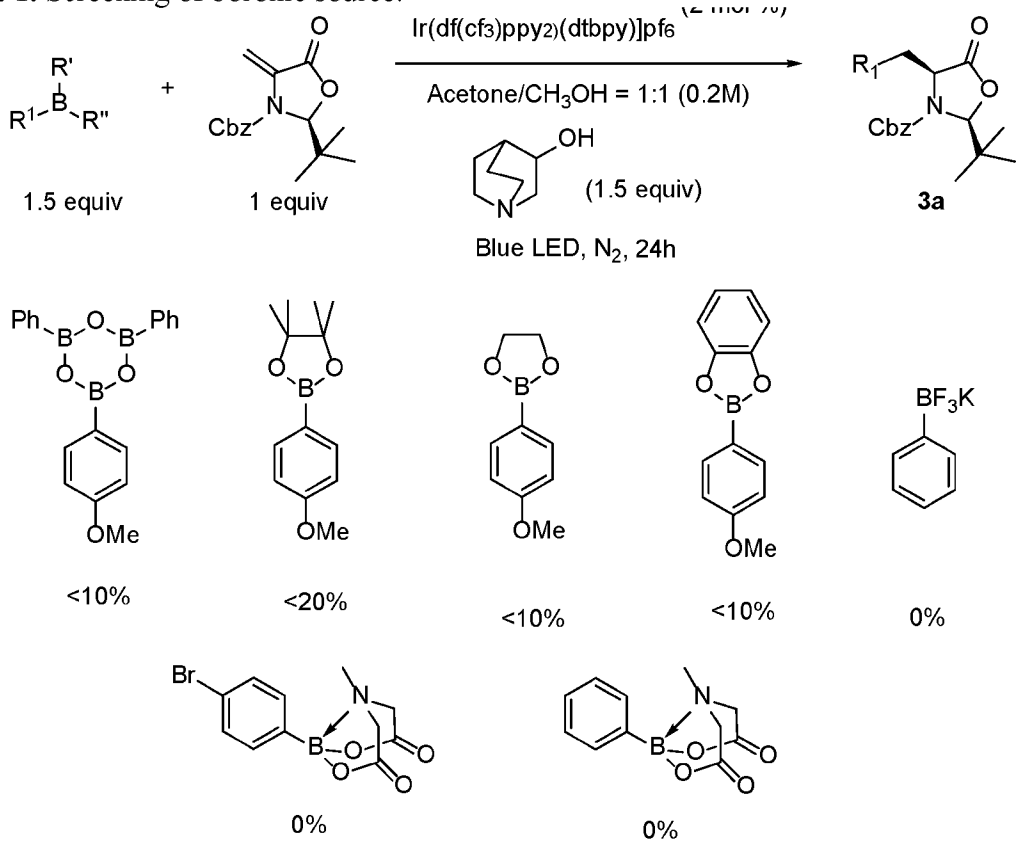
1 2 3a 5

Entry	Base	Solvent and D source	Time	Yield, D-content	Notes
1	1.5 eq Quinuclidinol	Acetone/MeOH=1:1 (0.2M) 80 eq D_2O	24h	55%, 52%	40w Blue LED
2	1.5 eq Quinuclidinol	Acetone/MeOH=1:1 (0.2M) 250 eq D_2O	24h	56%, 81%	40w Blue LED
3	1.5 eq Quinuclidinol	Acetone (0.2M) 80 eq D_2O	24h	25%, 47%	40w Blue LED

[a]Yield is calculated after isolation. [b]First dissolve Lewis base and boric acid in D source/Acetone/CH_3OD and stir for 1h. **5** is detected by LC-MS.

[00142] It was found that pretreated **1a** with quinuclidin-3-ol in solvent and D_2O could increase the deuterium incorporation efficiency (entry 12). In addition, probed boronic esters, boroxines, Molander borate salts etc. were also probed, but gave inferior results (**Scheme 1**).

Scheme 1. Screening of boronic source.[a, b]



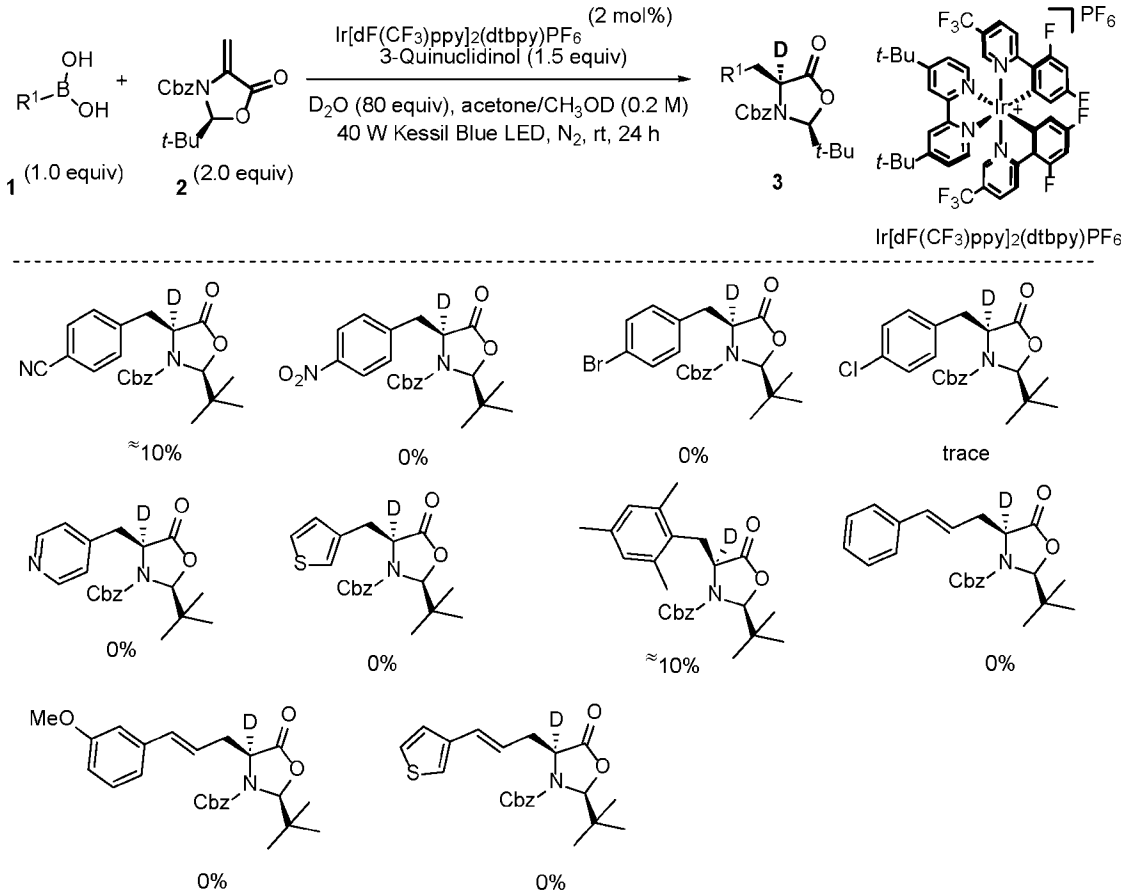
[a]Yield is estimated from TLC plate. [b]**3a** is detected by LC-MS.

2.3 Additional Substrate Scope:

[00143] After evaluation the reaction conditions, the scope of the process was explored. Arylboronic acids as radical precursors were tested firstly with chiral (*S*)-oxazolidinone **2**. The reaction could deliver aryl side chain contained chiral α-amino acid derivatives, which cannot be accessed by photoredox mediated decarboxylative approaches. The results of the study revealed that thiomethyl, acetamido and phenyl substituted phenylboronic acid worked smoothly under the standard conditions and generated useful aromatic amino acids **3b**-**3d** (**FIG. 2**). Excellent diastereoselectivity and high deuterium incorporation were achieved in these cases. Notably, the process provides a viable approach to accessing deuterated 4-mercapto-L-phenylalanine, a substrate particularly valuable for the study of catalytic mechanism of tyrosine *O*-prenyltransferase SirD. For the synthesis of **3e**, poor yield was obtained under the reaction conditions. It was found

the addition of 0.30 equiv of CsF could improve the yield from 36% to 51% without deteriorating dr and deuteration level. It was also realized that the protocol was sensitive to electronic and steric effects. Low yields were obtained for aryl boronic acids which bear electron-withdrawing groups and sterically hindered substrates presumably due to reduced reactivity (**Scheme 2**).

Scheme 2. Additional Substrate Scope[a]



[a]Yield is estimated from TLC plate. 0% means not detected by LC-MS.

[00144] In addition, no reaction occurred with alkenyl boronic acids (**Scheme 2**). However, the strategy could be applied for the synthesis of alkyl substituted α-deuterated amino acid derivatives with better yields presumably owing to higher reactivity. First, primary alkylboronic acids were examined as alkyl radical progenitors. It is noted that it has been challenging for the alkyl radicals to be generated by photoredox decarboxylative methods. As shown in **3f** and **3g**, good yields and high level of D-incorporation were obtained with the protocol. Next, the cyclic secondary alkyl radicals containing various rings (e.g., five-, six-, and seven-membered rings) were probed. The

steric hindrance did not affect the yield (71-82%), deuteration level (95-98%) and diastereoselectivity (>20:1 dr) in the examples of **3h-3l**. A similar trend was observed for acyclic secondary alkylboronic acid, which leads to a viable method for the synthesis of α-deuterated natural amino acid L-leucine (**3m**). This study was further expanded to the sterically demanding tertiary alkylboronic acids. The tested tertiary alkylboronic acids including an adamantyl group and analogue (**3n**, **3o**) or a *tert*-butyl group bearing various functional groups (**3p-3t**) furnished the corresponding products in good to excellent yield and with uniformly high diastereoselectivity (>20:1 dr) and high deuteration level (95-98%). It is noted that under the mild reaction conditions broad functional groups such as protected amines (**3c**, **3d**, **3g**, **3k**, and **3q**), alkene (**3t**), ester (**3s**), ether (**3a**), thioether (**3b**) and fluorine (**3l**) can be tolerated.

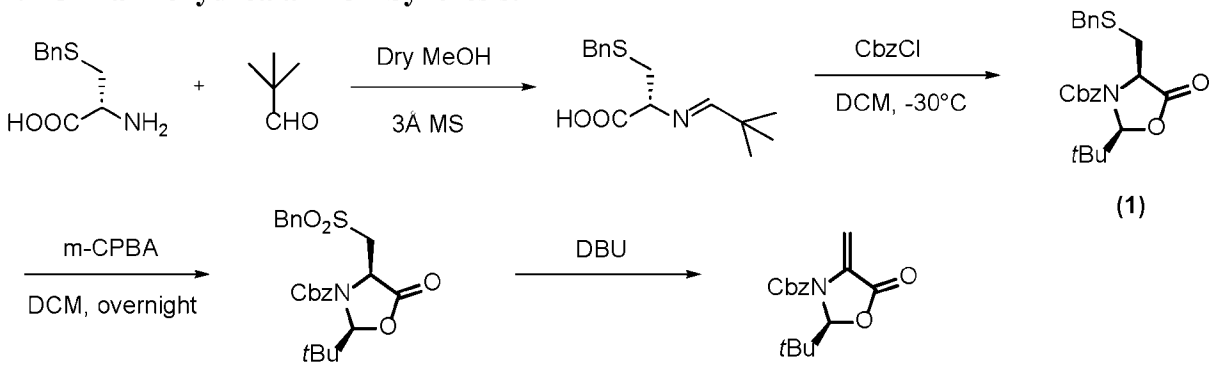
[00145] Finally, it was demonstrated that the method can be used for late-stage modification of complex biologically active molecules including saccharides (**3u** and **3v**), ibuprofen (**3w**), and dipeptide (**3x**). In these cases, the desired products were formed in good yields (43-71%) and with excellent dr (> 20:1) and high level of deuterium incorporation efficiency (**FIG. 3**). Smooth transformation of the synthesized products 3 into α-deuterated α-amino acids is demonstrated in the synthesis of α-deuterated L-Leu (**4m**) by reacting with conc. HCl for 45 min without the loss of the deuteration level (**FIG. 3**).

2.4 Procedures of Synthesis of 3k in 1.5 mmol:

[00146] To an oven-dried 100 mL-Schlenk tube equipped with a stir bar, were added boronic acid **1** (1.5 mmol, 1.0 equiv), and Lewis base (2.25 mmol, 1.5 equiv). Then acetone/CH_3OD (1:1 v/v, 0.2M, 3.75 mL) and 80 equiv. D_2O was added using a syringe. The solution was then stirred at rt for 1 h. After pretreated of **1** and **2**, chiral dehydroalanine (3.0 mmol, 2.0 equiv) and $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2 mol %) dissolved in acetone/CH_3OD (1:1 v/v, 0.2M, 3.75 mL) was added using a syringe. The technique "freeze-pump-thaw" (three times) was applied to the reaction system to remove the oxygen. The solution was then stirred at room temperature under the irradiation of two 40 W Kessil Blue LEDs for 24 h using electronic fan to cool the tube. The distance between Blue LEDs and solution is 1-2 cm. After completion of the reaction, 20 mL of water was added and extracted by EtOAc. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The product **3k** was purified by

column chromatography on silica gel eluting with hexane/ethyl acetate (4:1) as colorless oil about 577 mg (81%).

2.5 Chiral Dehydroalanine 2 Synthesis:



[00147] Benzyl (*2S,4R*)-4-((benzylthio)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (1):[1] To a round bottom flask equipped with a stir bar was added *S*-benzyl-L-cysteine (5 g, 23.5 mmol, 1 equiv.), NaOH (0.9g, 23.5 mmol, 0.95 equiv), and anhydrous MeOH (250 mL). The reaction was stirred at room temperature for 30 minutes. Trimethylacetaldehyde (3.09 mL, 28.5 mmol, 1.2 equiv) and activated 3 Å molecular sieves (25 g) were added to the reaction flask, each in one portion. The reaction was placed under nitrogen atmosphere and stirred at room temperature until the starting material had been consumed (determined by ^{1}H NMR of a filtered and concentrated aliquot of the reaction solution dissolved in CD_3OD). The reaction was quickly filtered through celite and concentrated by rotary evaporation. The residue was dried under high vacuum for 24 hours to afford the imine as a white solid. The imine was dissolved in anhydrous DCM (250 mL) and cooled to −30 °C. Benzyl chloroformate (5.05 mL, 35.5 mmol, 1.5 equiv) was added to the reaction dropwise via syringe. The reaction was allowed to reach 0 °C. The reaction was stirred for a full 18 hours then warmed to room temperature and stirred for an additional 6 hours. The mixture was washed with 1 M aqueous NaOH (1x 125 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (0%–10% ethyl acetate/hexanes) to afford the product (4.0 g, 40% yield) as a colorless oil. The physical properties and spectral data were consistent with the reported values.[1]

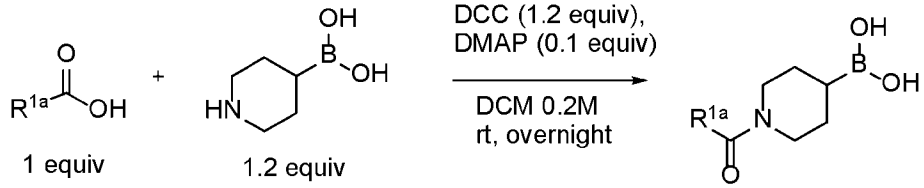
[00148] Benzyl (*2S,4R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxy-late (2):[1] To a round bottom flask equipped with a stir bar was added benzyl (*2S,4R*)-4-((benzylthio)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (3.15 g, 7.625 mmol, 1 equiv), meta-chloroperoxybenzoic acid (3.3 g, 19.06 mmol, 2.5 equiv), and DCM (100 mL). The reaction was stirred at room temperature for 18 hours. The reaction mixture was washed with 1 M aqueous sodium hydroxide (3 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (10%–30% ethyl acetate/hexanes) to afford the product (5.0 g, 74% yield) as a white foam. The physical properties and spectral data were consistent with the reported values.[1]

[00149] Benzyl (*S*)-2-(*tert*-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (3):[1] To a round bottom flask equipped with a stir bar was added (benzyl (*2S,4R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate) (2.75 g, 6.2 mmol, 1 equiv), and DCM (76 mL).The flask was chilled to 0 °C in an ice bath, and DBU (1.05 mL, 6.8 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred at 0 °C until the starting material had been consumed (determined by TLC, about 10 minutes). While still at 0 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride (25 mL), the layers were separated, and the organic phase was washed with saturated aqueous ammonium chloride (3x 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5%–10% ethyl acetate/hexanes) to afford the product (1.45 g, 83% yield) as a white solid. The physical properties and spectral data are consistent with the reported values.[1] Structure confirmed with previous data.[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 5H), 5.57 (s, 1H), 5.54 (s, 1H), 5.11 (d, J = 1.5 Hz, 2H), 0.79 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 134.7, 130.2, 128.9, 128.85, 128.82, 128.7, 104.3, 94.0, 68.8, 38.7, 24.3.

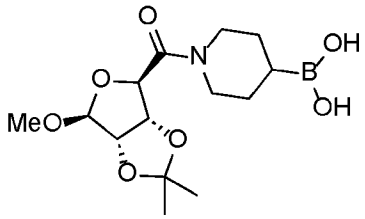
2.6 Synthesis of α-deuterated *Leu* (11):

[00150] To a round bottom flask equipped with a stir bar was added benzyl (*2S,4S*)-2-(*tert*-butyl)-4-isobutyl-5-oxooxazolidine-3-carboxylate (12 mg), and concentrated aqueous HCl (2 mL). The reaction was stirred at 80 °C with oil bath for 45 minutes then concentrated by rotary evaporation to afford the product (4.3 mg, 91%) as a white solid. The physical properties and spectral data are consistent with the values of commercially available *Leu*.

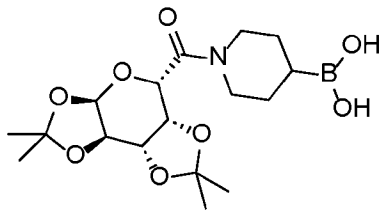
2.7 General Procedure for Synthesis of 1u-1x



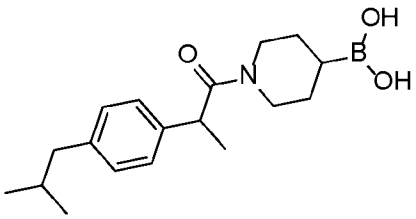
[00151] To an oven-dried round-bottom flask with a magnetic stir bar was added acid (0.8 mmol, 1.0 equiv.), piperidin-4-yl boronic acid (0.114 g, 0.88 mmol, 1.2 equiv.), DCC (0.198 g, 0.96 mmol, 1.2 equiv.) and DMAP (0.098 g, 0.80 mmol, 0.1 equiv.). Dry dichloromethane (4 mL) was added and the mixture was allowed to stir at room temperature until the acid was consumed (followed by TLC). Typical reaction times were between 0.5 h and 12 h. The white precipitates were filtered off and the solvent was removed under reduced pressure. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexane/ethyl acetate or hexane/dichloromethane.



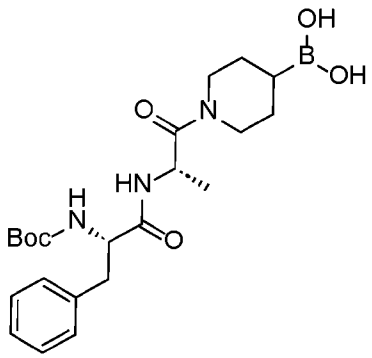
[00152] (1-((3aR,4R,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbonyl)piperidin-4-yl)boronic acid (1u): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (6:1) as white soild about 223 mg (85%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 (dd, J = 5.9, 1.1 Hz, 1H), 5.05 (s, 1H), 4.65 (d, J = 1.0 Hz, 1H), 4.56 (d, J = 5.9 Hz, 1H), 3.74 (s, 2H), 3.41 (s, 3H), 2.46 (m, 2H), 1.74 – 1.70 (m, 2H), 1.62 – 1.57 (m, 3H), 1.47 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 113.0, 109.8, 84.2, 83.7, 82.2, 55.8, 49.1(2C), 37.6 26.3, 24.9. 16.5(2C).HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{25}BNO_7$: 330.1719, found: 330.1712.



[00153] (1-((3aR,5S,5aR,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-carbonyl)piperidin-4-yl)boronic acid (1v): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (6:1) as white solid about 260 mg (84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (d, J = 4.8 Hz, 1H), 4.68 (dd, J = 7.7, 2.6 Hz, 1H), 4.66 (dd, J = 7.7, 2.1 Hz, 1H), 4.44 (d, J = 2.1 Hz, 1H), 4.38 (dd, J = 4.9, 2.6 Hz, 1H), 3.71 (s, 2H), 2.62 (m, 2H), 1.80 – 1.76 (m, 2H), 1.70 – 1.59 (m, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.32 (d, J = 5.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 110.1, 109.6, 96.3, 71.5, 70.6, 70.5, 68.3, 48.2(2C), 37.1, 26.0, 25.9, 24.8, 24.3, 15.4(2C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{29}BNO_8$: 386.1981, found: 386.1978.

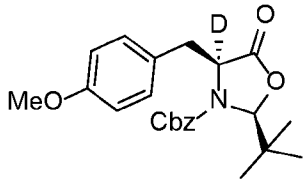


[00154] (1-(2-(4-Isobutylphenyl)propanoyl)piperidin-4-yl)boronic acid (1w): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (7:1) as white solid about 204 mg (80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 3.80 (s, 2H), 3.65 – 3.62 (m, 1H), 2.72 (d, J = 7.2 Hz, 2H), 2.45 (s, 2H), 1.89 (dq, J = 13.5, 6.8 Hz, 1H), 1.72 – 1.68 (m, 2H), 1.63 – 1.60 (m, 3H), 1.50 – 1.48 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 140.7, 136.6, 129.8 (2C), 127.4 (2C), 45.3, 45.1 (2C), 42.1, 32.8, 30.3, 22.5 (2C), 18.7 (2C), 14.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{29}BNO_3$: 318.2235, found: 318.2230.

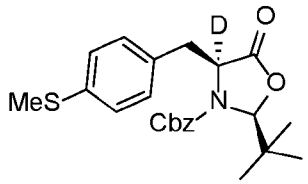


[00155] 1-((tert-Butoxycarbonyl)-L-phenylalanyl-L-alanyl)piperidin-4-yl)boronic acid (1x): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (3:1) as white soild about 22 mg (63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.14 (m, 5H), 4.53 (dd, J = 9.9, 5.0 Hz, 1H), 4.39 (q, J = 7.2 Hz, 1H), 3.87 (s, 2H), 3.02 (q, J = 7.7 Hz, 2H), 2.41 (s, 2H), 1.67 – 1.60 (m, 2H), 1.54 – 1.50 (m, 3H), 1.26 (s, 9H), 1.25 – 1.19 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.8, 155.5, 135.8, 129.3 (2C), 128.7 (2C), 127.0, 80.3, 60.5, 48.4, 48.2 (2C), 40.8, 38.9, 28.3 (3C), 18.0, 14.2 (2C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{35}BN_3O_6$: 448.2613, found: 448.2607.

3. Example Compound Characterization Data

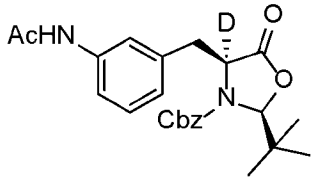


[00156] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(4-methoxybenzyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3a): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (6:1) as colorless oil about 23 mg (57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (q, J = 4.5 Hz, 5H), 7.11 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.42 (s, 1H), 5.04 (s, 2H), 4.19 (s, 0.05H), 3.87 (s, 3H), 3.23 (d, J = 14.2 Hz, 1H), 2.89 (d, J = 14.1 Hz, 1H), 0.84 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ172.5, 162.3, 155.9, 140.6, 137.8, 135.3, 130.5, 128.72 (2C), 128.66 (2C), 128.5, 126.2, 114.3, 96.2, 68.3, 53.2 (t), 37.0, 34.7, 29.7, 24.9 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{27}DNO_5$: 399.2025, found: 399.2020.

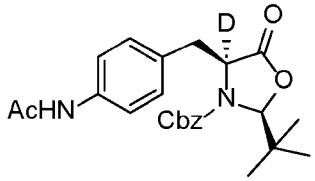


[00157] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(4-(methylthio)benzyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3b): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (6:1) as

colorless oil about 18 mg (47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.30 – 7.17 (m, 5H), 5.43 (s, 1H), 5.05 (s, 2H), 4.16 (s, 0.06H), 3.29 (d, J = 14.3 Hz, 1H), 2.98 (d, J = 14.3 Hz, 1H), 2.51 (s, 3H), 0.84 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 155.9, 141.1, 137.8, 135.3, 134.7, 129.2, 128.72 (2C), 128.66 (2C), 128.5 (2C), 126.2, 96.2, 68.3, 53.8 (t), 37.0, 29.7, 24.9 (3C), 15.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{27}DNO_4S$: 415.1796, found: 415.1793.

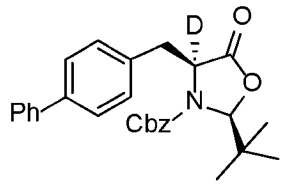


[00158] Benzyl (*2S,4S*)-4-(3-acetamidobenzyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3c): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 18 mg (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.30 – 7.20 (m, 5H), 7.08 (t, J = 7.7 Hz, 1H), 5.43 (s, 1H), 5.05 (s, 2H), 4.15 (s, 0.06H), 3.24 (d, J = 14.1 Hz, 1H), 2.89 (d, J = 14.1 Hz, 1H), 1.94 (s, 3H), 0.84 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 169.6, 156.0, 139.0, 136.3, 135.2, 130.1, 129.4, 128.7 (2C), 127.3 (2C), 121.3, 120.0, 118.1, 96.2, 68.4, 56.6-56.1 (m), 36.5, 31.9, 25.0 (3C), 24.9.HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{28}DN_2O_5$: 426.2134, found: 426.2128.

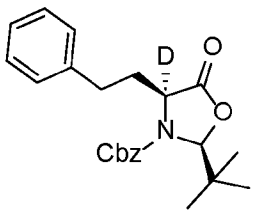


[00159] Benzyl (*2S,4S*)-4-(4-acetamidobenzyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3d): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 16 mg (49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.40 – 7.30 (m, 5H), 5.53 (s, 1H), 5.15 (s, 2H), 4.18 (s, 0.05H), 3.34 (d, J = 14.4 Hz, 1H), 2.99 (d, J = 14.4 Hz, 1H), 2.06 (s, 3H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 172.3, 169.8, 156.2, 139.2, 136.4, 135.4, 130.2 (2C), 129.5, 128.8 (2C), 127.5 (2C), 118.2 (2C),

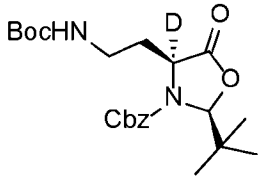
96.2, 67.2, 56.7-56.3 (m), 36.7, 32.0, 25.1, 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{28}DN_2O_5$: 426.2134, found: 426.2130.



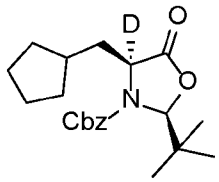
[00160] Benzyl (*2S,4S*)-4-([1,1'-biphenyl]-4-ylmethyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3e): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as white solid about 20 mg (51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 8.1 Hz, 2H), 7.82 – 7.56 (m, 7H), 7.54 – 7.40 (m, 5H), 5.61 (s, 1H), 5.23 (s, 2H), 4.20 (s, 0.06H), 3.42 (d, J = 14.1 Hz, 1H), 3.07 (d, J = 14.1 Hz, 1H), 1.02 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 155.6, 138.6, 137.6, 135.8, 134.8, 129.7, 128.9, 128.28 (2C), 128.27 (2C), 128.26 (2C), 127.5 (2C), 127.0, 125.9, 117.7 (2C), 96.2, 68.0, 56.2-55.7(m), 39.2, 36.1, 24.6 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{29}DNO_4$: 445.2232, found: 445.2229.



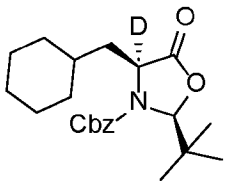
[00161] Benzyl (*2S,4S*)-2-(*tert*-butyl)-5-oxo-4-phenethyloxazolidine-3-carboxylate-4-*d* (3f): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 32 mg (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 3H), 7.17 (dd, J = 9.0, 3.7 Hz, 2H), 7.13 (d, J = 7.4 Hz, 2H), 7.09 – 7.02 (m, 3H), 5.42 (s, 1H), 5.01 (s, 2H), 4.53 (s, 0.03H), 2.94 – 2.64 (m, 2H), 2.14 – 1.91 (m, 2H), 0.84 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 155.9, 140.6, 135.3, 128.72 (2C), 128.66 (2C), 128.5 (4C), 126.2 (2C), 96.3, 68.3, 56.4-56.2 (m) 37.0, 34.7, 32.3, 24.9 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{26}DNNaO_4$: 405.1895, found: 405.1893.



[00162] Benzyl (*2S,4S*)-4-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3g): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 21 mg (41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 5.44 (s, 1H), 5.06 (d, J = 2.6 Hz, 2H), 4.23 (s, 0.08H), 3.09 – 2.90 (m, 1H), 1.98 (dd, J = 13.1, 6.2 Hz, 1H), 1.30 (s, 9H), 0.81 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 156.4, 155.8, 135.0, 128.9, 128.8 (2C), 128.6 (2C), 96.6, 79.2, 68.7, 55.6 (t), 37.3, 36.9, 33.1, 28.4 (3C), 24.9 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{31}DN_2NaO_6$: 444.2215, found: 444.2213.

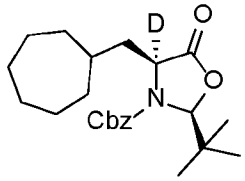


[00163] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(cyclopentylmethyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3h): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 24 mg (77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (q, J = 4.5 Hz, 5H), 5.42 (s, 1H), 5.04 (s, 2H), 4.16 (s, 0.05H), 2.06 (dq, J = 15.6, 7.8 Hz, 1H), 1.83 (dd, J = 13.5, 6.2 Hz, 1H), 1.63 (dd, J = 13.5, 8.8 Hz, 3H), 1.37 (dd, J = 14.8, 7.5 Hz, 4H), 1.03 – 0.92 (m, 2H), 0.84 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 156.0, 135.2, 128.69 (2C), 128.68 (2C), 96.3, 68.4, 56.6-56.1 (m), 39.6, 37.0, 36.5, 32.9, 31.9 (2C), 25.1, 25.0, 24.9 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{28}DNNaO_4$: 383.2052, found: 383.2051.

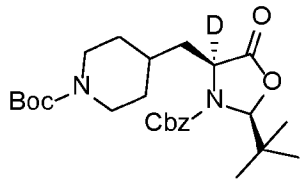


[00164] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(cyclohexylmethyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3i): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (6:1) as colorless oil about 28 mg (80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (hept, J = 3.0 Hz, 5H), 5.43 (s, 1H), 5.13 – 4.93 (m, 2H), 4.23 (s, 0.02), 1.64 (q, J = 8.8 Hz, 3H), 1.56 – 1.44 (m, 5H), 1.11 – 0.95 (m, 3H), 0.84 (s, 9H), 0.80 – 0.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 156.0, 135.2, 128.69 (2C), 128.68 (2C), 96.3, 68.4, 54.7 (t), 41.1, 36.9, 34.2, 33.4 (2C), 32.8, 26.4, 25.98,

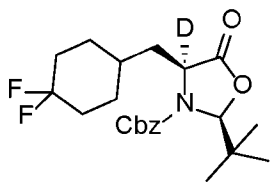
25.95, 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{30}DNNaO_4$: 397.2208, found: 397.2204.



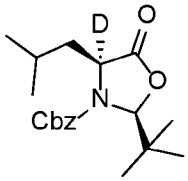
[00165] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(cycloheptylmethyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3j): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 29 mg (74%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (q, J = 4.6 Hz, 5H), 5.42 (s, 1H), 5.11 – 4.96 (m, 2H), 4.19 (s, 0.03), 1.75 (dd, J = 8.3, 4.0 Hz, 1H), 1.68 – 1.52 (m, 4H), 1.48 – 1.17 (m, 8H), 1.11 – 0.98 (m, 2H), 0.84 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 156.1, 135.2, 128.7 (4C), 96.3, 68.4, 55.4 (t), 41.4, 36.9, 35.6, 34.6, 33.8, 28.51 (2C), 28.48 (2C), 26.0, 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{33}DNO_4$: 389.2545, found: 389.2540.



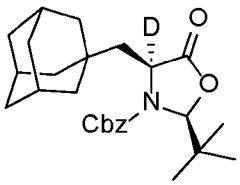
[00166] Benzyl (*2S,4S*)-4-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3k): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (3:1) as colorless oil about 35 mg (82%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 5H), 5.43 (s, 1H), 5.07 – 4.95 (m, 2H), 4.21 (s, 0.05H), 3.85 (s, 2H), 2.53 – 2.33 (m, 2H), 1.75 – 1.59 (m, 3H), 1.32 (s, 9H), 1.00 – 0.90 (m, 2H), 0.83 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 155.9, 154.7, 135.0, 128.84 (2C), 128.77 (2C), 128.73, 96.4, 79.2, 68.5, 54.5 (t), 40.1 (2C), 36.9, 32.8, 32.2 (2C), 31.7, 28.5 (3C), 24.9 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{37}DN_2NaO_6$: 498.2685, found: 498.2681.



[00167] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-((4,4-difluorocyclohexyl)methyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3l): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (7:1) as colorless oil about 32 mg (71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.15 (m, 5H), 5.42 (s, 1H), 5.01 (s, 2H), 4.17 (s, 0.04H), 1.87 – 1.48 (m, 9H), 1.17 – 1.00 (m, 2H), 0.82 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 156.0, 135.0, 128.9, 128.81 (2C), 128.78 (2C), 123.4 (dd, J = 240.7, 239.4 Hz, 1C), 96.4, 68.7, 54.7 (t), 39.3, 37.0, 33.1 (dd, J = 12.6, 12.4 Hz, 2C), 28.8 (dd, J = 10.1, 8.8 Hz, 2C), 25.4, 24.9 (3C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -91.98 (d, J = 235.5 Hz), -101.95 (d, J = 235.5 Hz). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{28}DF_2NNaO_4$: 433.2020, found: 433.2014.

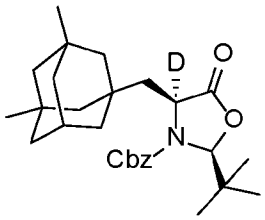


[00168] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-isobutyl-5-oxooxazolidine-3-carboxylate-4-*d* (3m): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (8:1) as colorless oil about 28 mg (86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (q, J = 5.8 Hz, 5H), 5.53 (s, 1H), 5.17 – 5.11 (m, 2H), 4.30 (s, 0.03H), 1.96 (dd, J = 13.5, 6.9 Hz, 1H), 1.76 (dd, J = 13.7, 6.3 Hz, 1H), 1.62 (dd, J = 13.6, 7.9 Hz, 1H), 0.97 – 0.87 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 156.7, 135.2, 128.69 (2C), 128.68 (2C), 128.5, 96.4, 68.5, 54.7 (t), 42.6, 36.9, 25.0 (3C), 22.8 (2C), 21.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{26}DNNaO_4$: 357.1895, found: 357.1895.

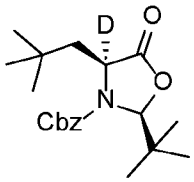


[00169] Benzyl (*2S,4S*)-4-(((*3S,5S,7S*)-adamantan-1-yl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3n): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (8:1) as light colorless oil about 36 mg (70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 5H), 5.42 (s, 1H), 5.08 – 4.97 (m, 2H), 4.30 (s, 0.02H), 1.77 (s, 2H), 1.63 (s, 1H), 1.53 (d, J = 11.8 Hz, 3H), 1.45 (s, 6H), 1.37 (d, J = 14.1 Hz, 5H), 0.83 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 155.7,

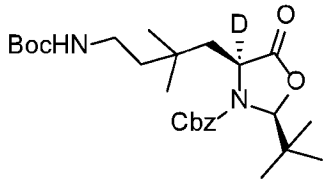
135.2, 129.0, 128.73 (2C), 128.65 (2C), 95.9, 68.4, 52.3 (t), 49.2, 42.4 (3C), 37.0, 36.8 (3C), 32.7, 28.5 (3C), 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{35}DNO_4$: 427.2702, found: 427.2694.



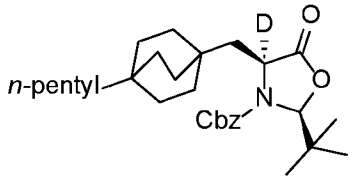
[00170] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(((*1r,3R,5S,7S*)-3,5-dimethyladamantan-1-yl)methyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3o): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (8:1) as white soild about 35 mg (63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 5H), 5.41 (s, 1H), 5.11 – 4.97 (m, 2H), 4.30 (s, 0.02H), 1.66 (d, J = 14.3 Hz, 1H), 1.43 (d, J = 14.3 Hz, 1H), 1.31 (s, 1H), 1.23 (s, 1H), 1.21 (s, 1H), 1.14 (d, J = 10.4 Hz, 5H), 1.06 (s, 2H), 0.98 (d, J = 13.1 Hz, 2H), 0.90 (d, J = 12.1 Hz, 1H), 0.82 (s, 9H), 0.64 (d, J = 3.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 155.7, 135.3, 128.9 (2C), 128.7 (2C), 95.9, 68.2, 52.6 (t), 51.0, 48.8, 48.7, 48.5 (2C), 43.05, 43.02, 40.8, 37.0, 34.4, 31.2, 30.7 (2C), 29.6 (2C), 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{38}DNNaO_4$: 477.2834, found: 477.2831.



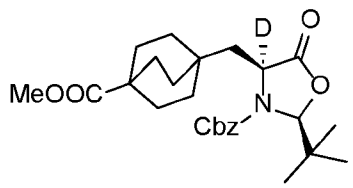
[00171] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-neopentyl-5-oxooxazolidine-3-carboxylate-4-*d* (3p): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (9:1) as colorless oil about 21 mg (65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.53 (s, 1H), 5.22 – 5.06 (m, 2H), 4.34 (s, 0.04H), 1.87 (d, J = 14.2 Hz, 1H), 1.64 (d, J = 14.2 Hz, 1H), 0.96 (s, 9H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 155.8, 135.4, 128.9 (3C), 128.7 (2C), 96.1, 68.3, 53.7 (t), 48.1, 36.9, 30.9, 29.7 (3C), 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{28}DNNaO_4$: 371.2052, found: 371.2051.



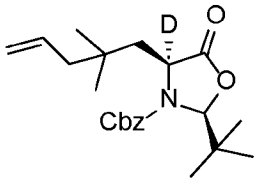
[00172] 5-Benzyl (*2S,4S*)-4-(4-((*tert*-butoxycarbonyl)amino)-2,2-dimethylbutyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3q): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as colorless oil about 33 mg (51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 5H), 5.42 (s, 1H), 5.04 (q, J = 11.8 Hz, 2H), 4.34 (s, 1H), 4.23 (s, 0.03H), 3.05 – 2.85 (m, 2H), 1.81 (d, J = 14.4 Hz, 1H), 1.52 (s, 1H), 1.32 (s, 11H), 0.84 (d, J = 7.7 Hz, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 156.0, 155.7, 135.1, 128.9, 128.8 (2C), 128.7 (2C), 96.1, 79.0, 68.4, 53.8-53.5 (m), 46.3, 41.2, 36.9, 36.7, 32.8, 28.5 (3C), 27.3, 27.2, 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{40}DN_2O_6$: 478.3022, found: 478.3015.



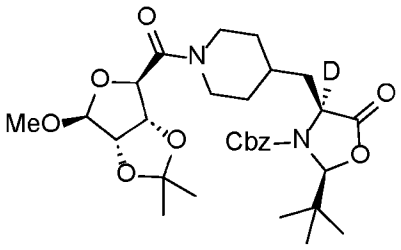
[00173] Benzyl (*2S,4S*)-2-(*tert*-butyl)-5-oxo-4-((4-pentylbicyclo[2.2.2]octan-1-yl)methyl)oxazolidine-3-carboxylate-4-*d* (3r): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (8:1) as white solid about 28 mg (51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (q, J = 5.6 Hz, 5H), 5.41 (s, 1H), 5.07 – 4.94 (m, 2H), 4.20 (s, 0.05H), 1.66 (s, 1H), 1.41 (d, J = 14.4 Hz, 1H), 1.37 – 1.22 (m, 5H), 1.16 (dt, J = 14.2, 6.6 Hz, 8H), 1.10 – 0.97 (m, 5H), 0.91 – 0.86 (m, 2H), 0.82 (s, 9H), 0.75 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 155.7, 135.1, 129.0, 128.74 (2C), 128.68 (2C), 96.0, 68.4, 53.2 (t), 46.4, 41.7, 36.9, 32.9, 31.4 (2C), 31.2 (2C), 31.1 (2C), 30.5, 29.7, 25.0 (3C), 23.3, 22.7, 14.1. HRMS (ESI-TOF) m/z: $[M + Na]^-$ calcd for $C_{24}H_{31}DNNaO_4$: 493.3147, found: 493.3146.



[00174] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-((4-(methoxycarbonyl)bicyclo [2.2.2]octan-1-yl)methyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3s): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (7:1) as white solid about 27 mg (58%). ^{1}H NMR (500 MHz, CDCl3) δ 7.24 (h, J = 5.4 Hz, 5H), 5.40 (s, 1H), 5.05 – 4.95 (m, 2H), 4.21 (s, 0.04H), 3.49 (s, 3H), 1.66 (d, J = 14.4 Hz, 1H), 1.56 (t, J = 8.1 Hz, 6H), 1.43 (d, J = 14.4 Hz, 2H), 1.38 – 1.23 (m, 5H), 0.81 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 173.3, 155.7, 135.0, 129.1, 128.9 (2C), 128.7 (2C), 96.1, 68.6, 53.1 (t), 51.6, 46.0, 38.8, 36.9, 31.0, 30.4 (3C), 28.4 (3C), 24.9 (3C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{34}DNNaO_6$: 481.2419, found: 481.241.4.

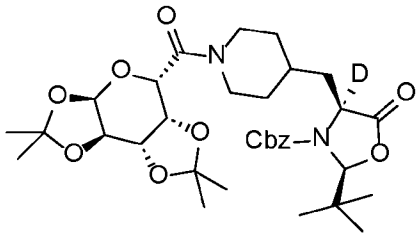


[00175] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-(2,2-dimethylpent-4-en-1-yl)-5-oxooxazolidine-3-carboxylate-4-*d* (3t): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (8:1) as colorless oil about 21 mg (47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 5H), 5.66 (dq, J = 17.2, 7.5 Hz, 1H), 5.43 (s, 1H), 5.05 (q, J = 11.9 Hz, 2H), 4.93 – 4.82 (m, 2H), 4.29 (s, 0.05H), 1.99 – 1.83 (m, 2H), 1.78 (d, J = 14.4 Hz, 1H), 1.54 (s, 1H), 0.85 (d, J = 10.9 Hz, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 155.8, 135.2, 135.0, 128.9, 128.74 (2C), 128.70 (2C), 117.5, 96.2, 68.4, 53.8 (t), 47.1, 46.4, 36.9, 33.5, 26.8, 26.6, 25.0 (3C). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{31}DNO_4$: 375.2389, found: 375.2387.

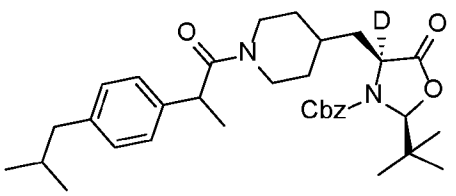


[00176] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-((1-((*3aR,4R,6S,6aS*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbonyl)piperidin-4-yl)methyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3u): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate

(4:1) as pare yellow oil about 36 mg (71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 5H), 5.43 (s, 1H), 5.17 (dd, J = 5.9, 1.1 Hz, 1H), 5.07 – 4.95 (m, 2H), 4.87 (s, 1H), 4.66 (d, J = 1.0 Hz, 1H), 4.55 (d, J = 5.9 Hz, 1H), 4.28 (s, 0.04H), 3.85 (s, 2H), 3.34 (s, 3H), 2.53 – 2.33 (m, 2H), 1.72 – 1.64 (m, 2H), 1.59 – 1.51 (m, 3H), 1.45 (s, 3H), 1.32 (s, 9H), 1.20 (s, 3H), 0.95 – 0.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 172.1, 156.0, 137.3, 131.4, 130.2, 127.0(2C), 113.0, 109.8, 107.8, 96.2, 84.2, 83.7, 82.2, 68.3, 55.8, 55.0, 53.4 (t), 45.9, 38.9, 33.0, 31.3, 30.6, 28.3, 26.3, 25.0 (3C), 16.0.HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{41}DN_2NaO_9$: 598.2845, found: 598.2840.

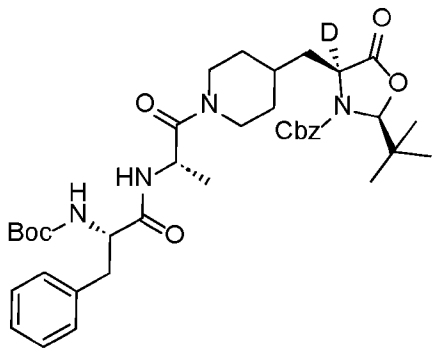


[00177] Benzyl (*2S,4S*)-2-(*tert*-butyl)-5-oxo-4-((1-((*3aR,5S,5aR,8aS,8bR*)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-carbonyl)piperidin-4-yl)methyl)oxazolidine-3-carboxylate-4-*d* (3v): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as white solid about 29 mg (68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 5H), 5.63 (d, J = 4.8 Hz, 1H), 5.36 (s, 1H), 5.01 – 4.89 (m, 2H), 4.68 (dd, J = 7.7, 2.6 Hz, 1H), 4.62 (dd, J = 7.7, 2.1 Hz, 1H), 4.44 (d, J = 2.1 Hz, 1H), 4.38 (dd, J = 4.9, 2.6 Hz, 1H), 4.14 (s, 0.03H), 3.79 (s, 2H), 2.53 – 2.27 (m, 2H), 1.69 – 1.53 (m, 2H), 1.51 – 1.42 (m, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.13 (s, 6H), 0.93 – 0.84 (m, 2H), 0.76 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 168.9, 154.1, 136.9, 131.1, 124.7 (2C), 123.8 (2C), 121.8, 119.1, 113.4, 96.5, 72.0, 70.6, 70.3, 68.7, 53.8 (t), 46.3 (2C), 38.3 (2C), 32.1, 30.2, 28.7 (3C), 26.0 (2C), 24.8 (2C), 14.2.HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{33}H_{45}DN_2NaO_{10}$: 654.3107, found: 654.3104.



[00178] Benzyl (*2S,4S*)-2-(*tert*-butyl)-4-((1-(2-(4-isobutylphenyl)propanoyl)piperidin-4-yl)methyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3w): The title product was prepared according

to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (4:1) as white solid about 27 mg (51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 5H), 7.16 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 5.43 (s, 1H), 5.07 – 4.95 (m, 2H), 4.20 (s, 0.03H), 3.85 (s, 2H), 3.65 – 3.63 (m, 1H), 2.72 (d, J = 7.2 Hz, 2H), 2.45 (s, 2H), 1.95 (dq, J = 13.5, 6.8 Hz, 1H), 1.75 – 1.59 (m, 2H), 1.58 – 1.50 (m, 3H), 1.40 (d, J = 7.2 Hz, 3H), 1.01 (d, J = 6.6 Hz, 6H), 0.92 (d, J = 8.8 Hz, 2H), 0.83 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 173.4, 155.9, 140.6, 137.7, 132.2, 129.4 (2C), 127.3 (2C), 125.1, 123.0 (2C), 122.1, 109.5, 96.2, 66.7, 53.0 (t), 45.2(2C), 45.0, 41.3, 39.2, 33.6, 30.2, 27.2 (2C), 22.4 (3C), 18.5 (2C), 13.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{34}H_{45}DN_2NaO_5$: 586.3362, found: 586.3358.



[00179] Benzyl (*2S,4S*)-4-((1-((*tert*-butoxycarbonyl)-L-phenylalanyl-L-alanyl)piperidin-4-yl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate-4-*d* (3x): The title product was prepared according to the general procedure and purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) as pare red soild about 59 mg (43%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 10H), 5.43 (s, 1H), 5.27 – 5.11 (m, 2H), 5.07 – 4.95 (m, 2H), 4.54 (q, J = 7.5 Hz, 1H), 4.39 (q, J = 7.2 Hz, 1H), 3.85 (s, 2H), 2.99 (q, J = 7.7 Hz, 1H), 2.53 – 2.33 (m, 2H), 1.72 – 1.61 (m, 2H), 1.58 – 1.50 (m, 3H), 1.32 (s, 9H), 1.23 – 1.08 (m, 3H), 0.96 – 0.90 (m, 1H), 0.83 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.9, 170.8, 155.5, 152.4, 136.6, 135.8, 129.4, 128.8 (2C), 128.7 (2C), 128.0, 127.0, 111.4, 102.41, 102.39, 96.2, 80.3, 68.2, 55.8, 55.6, 48.4, 48.2 (2C), 38.9, 38.4, 30.7 (2C), 29.7 (3C), 28.3, 21.1 (3C), 18.0, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{38}H_{51}DN_4NaO_8$: 716.3740, found: 716.3738.

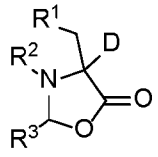
4. References

[00180] [1] a) Aycock, R. A.; Vogt, D. B.; Jui. N. T. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* **2017**, *8*, 7998-8003. b) Aycock, R. A.; Pratt, C. J.; Jui,

N. T. Aminoalkyl radicals as powerful intermediates for the synthesis of unnatural amino acids and peptides. *ACS Catal.* **2018**, *8*, 9115-9119. [2] Reich, D.; Trowbridge, A.; Gaunt, M. J. Rapid syntheses of (−)-FR901483 and (+)-TAN1251C enabled by complexity-generating photocatalytic olefin hydroaminoalkylation. *Angew. Chem., Int. Ed.* **2020**, *59*, 2256–2261.

[00181] For reasons of completeness, various aspects of the technology are set out in the following clauses:

Clause 1. A method for preparing a deuterated compound of formula (I), or a salt thereof,



(I),

wherein:

R^1 is G^1, C_{1-10}alkyl, $–L^1–R^Y$, or $–G^1\text{-}L^1–R^Y$;

R^2 is an amine protecting group, hydrogen, or C_{1-6}alkyl; and

R^3 is C_{1-6}alkyl or C_{1-4}haloalkyl;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, $–OC_{1-6}$alkyl, $–OG^{1a}$, $–OC_{1-4}$haloalkyl, –SH, $–SC_{1-6}$alkyl, $–SG^{1a}$, $–SC_{1-4}$haloalkyl, $–NH_2$, $–NHC_{1-4}$alkyl, $–NHG^{1a}$, $–N(C_{1-4}\text{alkyl})_2$, $–C(O)C_{1-4}$alkyl, $–C(O)G^{1a}$, $–C(O)OC_{1-4}$alkyl, $–C(O)OG^{1a}$, $–C(O)NH_2$, $–C(O)NHG^{1a}$, $–C(O)NHC_{1-4}$alkyl, $–C(O)N(C_{1-4}\text{alkyl})_2$, $–SO_2C_{1-4}$alkyl, $–SO_2G^{1a}$, $–SO_2NH_2$, $–SO_2NHC_{1-4}$alkyl, $–SO_2N(C_{1-4}\text{alkyl})_2$, $–C_{1-4}$alkylene–OH, $–C_{1-4}$alkylene–OC_{1-4}alkyl, $–C_{1-4}$alkylene–NH_2, $–C_{1-4}$alkylene–NHC_{1-4}alkyl, $–C_{1-4}$alkylene–$N(C_{1-4}\text{alkyl})_2$, –O–C_{1-4}alkylene–OH, –O–C_{1-4}alkylene–OC_{1-4}alkyl, –O–C_{1-4}alkylene–NH_2, –O–C_{1-4}alkylene–NHC_{1-4}alkyl, –O–C_{1-4}alkylene–$N(C_{1-4}\text{alkyl})_2$, and C_{1-3}alkylene–G^{1a}, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, $–NH_2$, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, $–SO_2C_{1-4}$alkyl, $–SO_2NH_2$, –SO_2NHC_{1-4}alkyl, and –SO_2N(C_{1-4}alkyl)$_2$;

L^1, at each occurrence, is a C_{1-10}alkylene, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with –O–, –S–, –SO–, $–SO_2–$, –C(O)–, –C(O)O–, –C(O)N(R^X)–, or –N(R^X)–, wherein 2 methylene groups replaced with –O–, –S–, –SO–, –C(O)O–, –C(O)N(R^X)–, $–SO_2–$, or –N(R^X)– are separated by two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with –Cy^1–;

Cy^1 is phenylene, C_{3-6}cycloalkylene, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, and halogen;

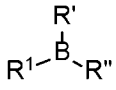
R^X is hydrogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, or –C_{1-3}alkylene–C_{3-4}cycloalkyl;

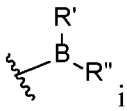
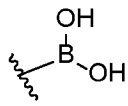
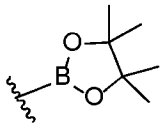
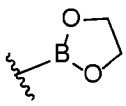
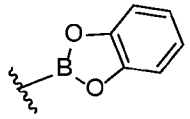
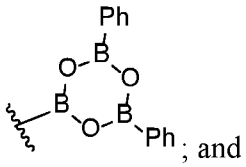
R^Y, at each occurrence, is C_{1-4}alkyl, C_{2-4}alkenyl, –OC_{1-4}alkyl, –OC_{1-4}haloalkyl, –OH, G^Y, –OG^Y, cyano, –SH, –SC_{1-4}alkyl, –SC_{1-4}haloalkyl, –SG^1, $–NH_2$, –NHC_{1-4}alkyl, –NHG^Y, –N(C_{1-4}alkyl)$_2$, –NHC(O)C_{1-4}alkyl, –NHC(O)OC_{1-4}alkyl, –C(O)C_{1-4}alkyl, –C(O)G^Y, –C(O)OG^Y, –C(O)OC_{1-4}alkyl, $–C(O)NH_2$, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –C(O)NHG^Y, –C(O)N(G^Y)$_2$, $–SO_2C_{1-4}$alkyl, –SO_2G^Y, $–SO_2NH_2$, –SO_2NHC_{1-4}alkyl, or –SO_2N(C_{1-4}alkyl)$_2$; and

G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, $–NH_2$, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, $–SO_2C_{1-4}$alkyl, $–SO_2NH_2$, –SO_2NHC_{1-4}alkyl, and –SO_2N(C_{1-4}alkyl)$_2$;

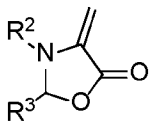
the method comprising:

mixing a compound of formula (III):


(III), wherein


is  ,  ,  ,  , or  ; and

a compound of formula (II),


(II),

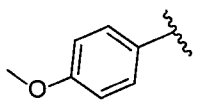
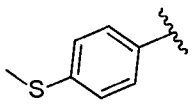
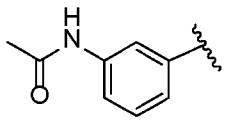
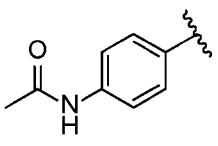
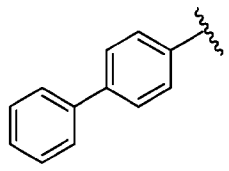
with a photocatalyst, a base, and D_2O to form a reaction mixture; and

exposing the reaction mixture to light, thereby producing the deuterated compound of formula (I).

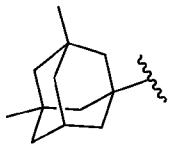
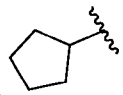
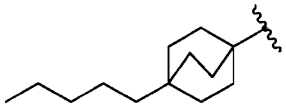
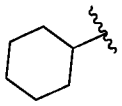
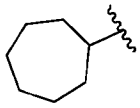
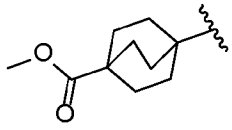
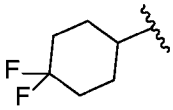
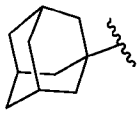
Clause 2. The method of clause 1, wherein R^1 is G^1.

Clause 3. The method of clause 2, wherein G^1 is the optionally substituted 6- to 12-membered aryl.

Clause 4. The method of clause 3, wherein the optionally substituted 6- to 12-membered aryl is optionally substituted phenyl.

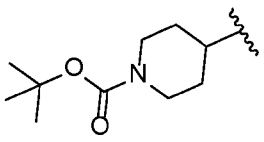
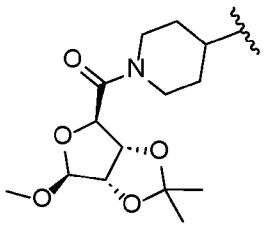
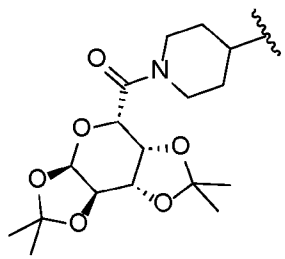
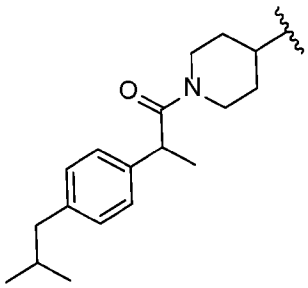
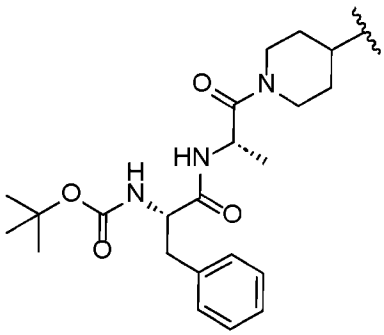
Clause 5. The method of clause 4, wherein G^1 is  ,  ,  ,  , or  .

Clause 6. The method of clause 2, wherein G^1 is the optionally substituted C_{3-10}carbocyclyl.

Clause 7. The method of clause 6, wherein G^1 is  ,  ,  ,  ,  ,  ,  , or  .

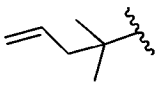
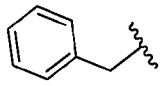
Clause 8. The method of clause 2, wherein G^1 is the optionally substituted 4- to 12-membered heterocyclyl.

Clause 9. The method of clause 8, wherein the optionally substituted 4- to 12-membered heterocyclyl is optionally substituted piperidinyl.

Clause 10. The method of clause 9, wherein G^1 is  ,  ,  ,  , or  .

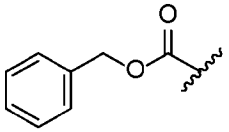
Clause 11. The method of clause 1, wherein R^1 is $C_{1\text{-}10}$alkyl or $-L^1-R^Y$.

Clause 12. The method of clause 11, wherein R^1 is  or  .

Clause 13. The method of clause 11, wherein R^1 is  or  .

Clause 14. The method of any one of clauses 1-13, wherein R^2 is the amine protecting group.

Clause 15. The method of claim 14, wherein the amine protecting group is

 (Cbz).

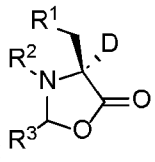
Clause 16. The method of any one of clauses 1-13, wherein R^2 is $C_{1\text{-}6}$alkyl.

Clause 17. The method of claim 16, wherein R^2 is $-CH_3$.

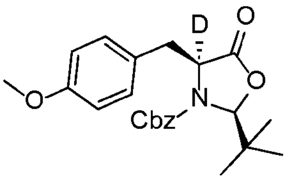
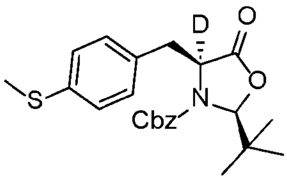
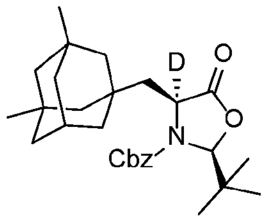
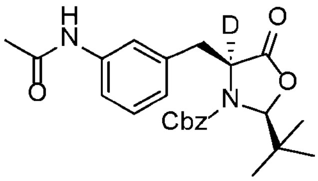
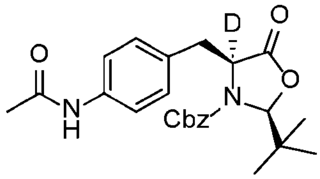
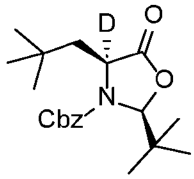
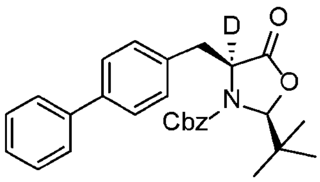
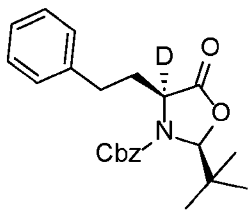
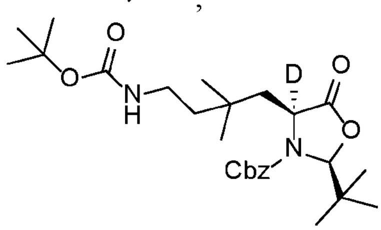
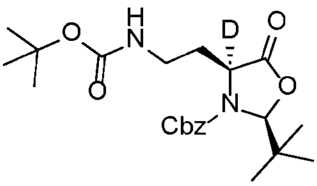
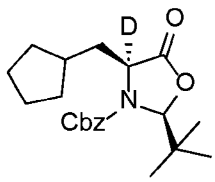
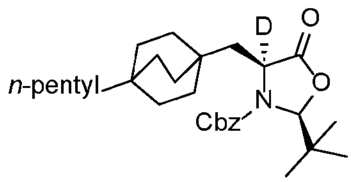
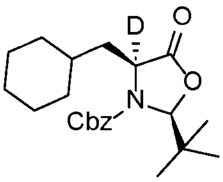
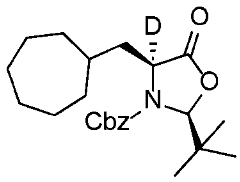
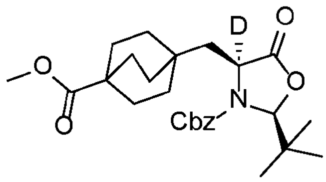
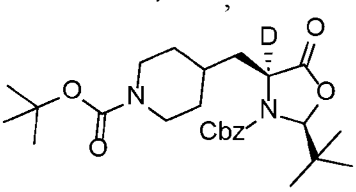
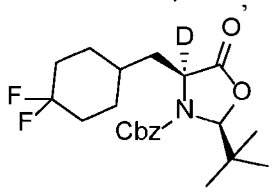
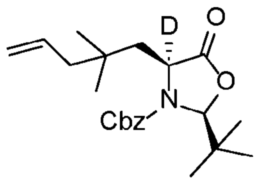
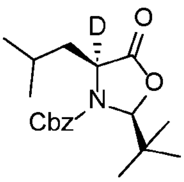
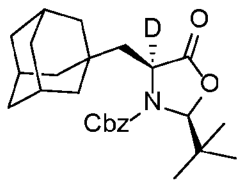
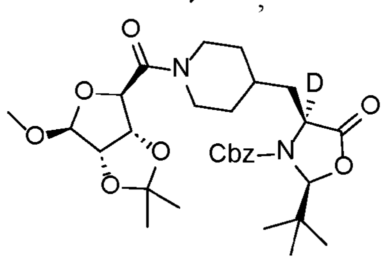
Clause 18. The method of claim 17, wherein each hydrogen in the $-CH_3$ is deuterium.

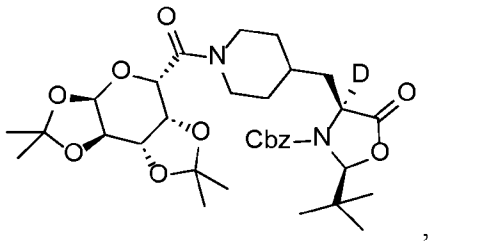
Clause 19. The method of any one of clauses 1-18, wherein R^3 is $C_{1\text{-}6}$alkyl.

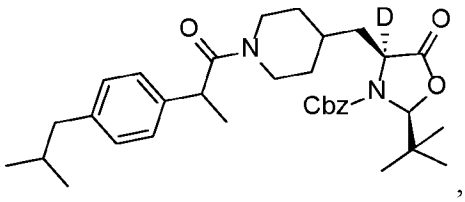
Clause 20. The method of claim 19, wherein R^3 is  .

Clause 21. The method of any one of clauses 1-20, wherein the compound of formula (I) is a compound of formula:  .

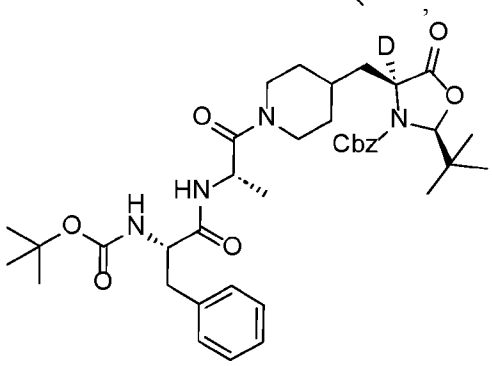
Clause 22. The method of any one of clauses 1-21, wherein the compound of formula (I) is

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,





, or

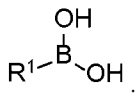


.

Clause 23. The method of any one of clauses 1-22, wherein the compound of formula (I) has at least 75% deuterium incorporation at each deuterium label.

Clause 24. The method of any one of clauses 1-22, wherein the compound of formula (I) has at least 90% deuterium incorporation at each deuterium label.

Clause 25. The method of any one of clauses 1-24, wherein the compound of formula (III) is



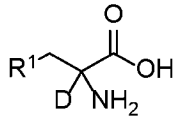
.

Clause 26. The method of any one of clauses 1-25, wherein the base is a Lewis base.

Clause 27. The method of any one of clauses 1-26, wherein the photocatalyst is an iridium (Ir)-based photocatalyst.

Clause 28. The method of any one of clauses 1-27, wherein the light is blue LED light.

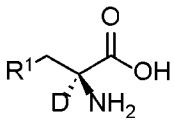
Clause 29. A method of preparing a deuterated compound of formula (I-AA), or a salt thereof,


(I-AA),

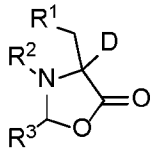
the method comprising:

preparing a deuterated compound of formula (I) according to the method of any one of clauses 1-28; then hydrolyzing the deuterated compound of formula (I).

Clause 30. The method of clause 29, wherein the deuterated compound of formula (I-AA) is


.

Clause 31. A deuterated compound of formula (I), or a salt thereof,


(I),

wherein:

R^1 is G^1, C_{1-10}alkyl, $-L^1-R^Y$, or $-G^1-L^1-R^Y$;

R^2 is an amine protecting group, hydrogen, or C_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{1-4}haloalkyl;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, $-OC_{1-6}$alkyl, $-OG^{1a}$, $-OC_{1-4}$haloalkyl, –SH, $-SC_{1-6}$alkyl, $-SG^{1a}$, $-SC_{1-4}$haloalkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-NHG^{1a}$, $-N(C_{1-4}alkyl)_2$, $-C(O)C_{1-4}$alkyl, $-C(O)G^{1a}$, $-C(O)OC_{1-4}$alkyl, $-C(O)OG^{1a}$, $-C(O)NH_2$, $-C(O)NHG^{1a}$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2G^{1a}$, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, $-SO_2N(C_{1-4}alkyl)_2$, $-C_{1-4}$alkylene–OH, $-C_{1-4}$alkylene–

OC_{1-4}alkyl, $-C_{1-4}$alkylene–NH_2, $-C_{1-4}$alkylene–NHC_{1-4}alkyl, $-C_{1-4}$alkylene–$N(C_{1-4}alkyl)_2$, –O–C_{1-4}alkylene–OH, –O–C_{1-4}alkylene–OC_{1-4}alkyl, –O–C_{1-4}alkylene–NH_2, –O–C_{1-4}alkylene–NHC_{1-4}alkyl, –O–C_{1-4}alkylene–$N(C_{1-4}alkyl)_2$, and C_{1-3}alkylene–G^{1a}, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, $-OC_{1-4}$alkyl, $-OC_{1-2}$haloalkyl, –SH, $-SC_{1-4}$alkyl, $-SC_{1-2}$haloalkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-C(O)C_{1-4}$alkyl, $-C(O)OC_{1-4}$alkyl,$-C(O)NH_2$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, and $-SO_2N(C_{1-4}alkyl)_2$;

L^1, at each occurrence, is a C_{1-10}alkylene, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with –O–, –S–, –SO–, $-SO_2-$, –C(O)–, –C(O)O–, $-C(O)N(R^X)-$, or $-N(R^X)-$, wherein 2 methylene groups replaced with –O–, –S–, –SO–, –C(O)O–, $-C(O)N(R^X)-$, $-SO_2-$, or $-N(R^X)-$ are separated by two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with $-Cy^1-$;

Cy^1 is phenylene, C_{3-6}cycloalkylene, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, and halogen;

R^X is hydrogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, or $-C_{1-3}$alkylene–C_{3-4}cycloalkyl;

R^Y, at each occurrence, is C_{1-4}alkyl, C_{2-4}alkenyl, $-OC_{1-4}$alkyl, $-OC_{1-4}$haloalkyl, –OH, G^Y, $-OG^Y$, cyano, –SH, $-SC_{1-4}$alkyl, $-SC_{1-4}$haloalkyl, $-SG^1$, $-NH_2$, $-NHC_{1-4}$alkyl, $-NHG^Y$, $-N(C_{1-4}alkyl)_2$, $-NHC(O)C_{1-4}$alkyl, $-NHC(O)OC_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)G^Y$, $-C(O)OG^Y$, $-C(O)OC_{1-4}$alkyl, $-C(O)NH_2$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-C(O)NHG^Y$, $-C(O)N(G^Y)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2G^Y$, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, or $-SO_2N(C_{1-4}alkyl)_2$; and

G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl,

C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –$N(C_{1-4}alkyl)_2$, –$C(O)C_{1-4}$alkyl, –$C(O)OC_{1-4}$alkyl,–$C(O)NH_2$, –$C(O)NHC_{1-4}$alkyl, –$C(O)N(C_{1-4}alkyl)_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –$SO_2N(C_{1-4}alkyl)_2$.

Clause 32. The compound of clause 31, or a salt thereof, wherein that compound has at least 50% deuterium incorporation at each deuterium label.

Clause 33. The compound of clause 31, or a salt thereof, wherein that compound has at least 75% deuterium incorporation at each deuterium label.

Clause 34. The compound of clause 31, or a salt thereof, wherein that compound has at least 90% deuterium incorporation at each deuterium label.

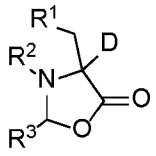
Clause 35. The compound of clause 31, or a salt thereof, wherein that compound has at least 95% deuterium incorporation at each deuterium label.

Clause 36. The compound of clause 31, or a salt thereof, wherein that compound has at least 99% deuterium incorporation at each deuterium label.

CLAIMS

What is claimed is:

1. A method for preparing a deuterated compound of formula (I), or a salt thereof,



(I),

wherein:

R^1 is G^1, C_{1-10}alkyl, $–L^1–R^Y$, or $–G^1\text{-}L^1–R^Y$;

R^2 is an amine protecting group, hydrogen, or C_{1-6}alkyl; and

R^3 is C_{1-6}alkyl or C_{1-4}haloalkyl;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, $–OC_{1-6}$alkyl, $–OG^{1a}$, $–OC_{1-4}$haloalkyl, –SH, $–SC_{1-6}$alkyl, $–SG^{1a}$, $–SC_{1-4}$haloalkyl, $–NH_2$, $–NHC_{1-4}$alkyl, $–NHG^{1a}$, $–N(C_{1-4}\text{alkyl})_2$, $–C(O)C_{1-4}$alkyl, $–C(O)G^{1a}$, $–C(O)OC_{1-4}$alkyl, $–C(O)OG^{1a}$, $–C(O)NH_2$, $–C(O)NHG^{1a}$, $–C(O)NHC_{1-4}$alkyl, $–C(O)N(C_{1-4}\text{alkyl})_2$, $–SO_2C_{1-4}$alkyl, $–SO_2G^{1a}$, $–SO_2NH_2$, $–SO_2NHC_{1-4}$alkyl, $–SO_2N(C_{1-4}\text{alkyl})_2$, $–C_{1-4}$alkylene–OH, $–C_{1-4}$alkylene–OC_{1-4}alkyl, $–C_{1-4}$alkylene–NH_2, $–C_{1-4}$alkylene–NHC_{1-4}alkyl, $–C_{1-4}$alkylene–$N(C_{1-4}\text{alkyl})_2$, –O–C_{1-4}alkylene–OH, –O–C_{1-4}alkylene–OC_{1-4}alkyl, –O–C_{1-4}alkylene–NH_2, –O–C_{1-4}alkylene–NHC_{1-4}alkyl, –O–C_{1-4}alkylene–$N(C_{1-4}\text{alkyl})_2$, and C_{1-3}alkylene–G^{1a}, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, $–OC_{1-4}$alkyl, $–OC_{1-2}$haloalkyl, –SH, $–SC_{1-4}$alkyl, $–SC_{1-2}$haloalkyl, $–NH_2$, $–NHC_{1-4}$alkyl, $–N(C_{1-4}\text{alkyl})_2$,

–C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –$SO_2N(C_{1-4}alkyl)_2$;

L^1, at each occurrence, is a C_{1-10}alkylene, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with –O–, –S–, –SO–, –SO_2–, –C(O)–, –C(O)O–, –C(O)N(R^X)–, or –N(R^X)–, wherein 2 methylene groups replaced with –O–, –S–, –SO–, –C(O)O–, –C(O)N(R^X)–, –SO_2–, or –N(R^X)– are separated by two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with –Cy^1–;

Cy^1 is phenylene, C_{3-6}cycloalkylene, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, and halogen;

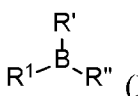
R^X is hydrogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, or –C_{1-3}alkylene–C_{3-4}cycloalkyl;

R^Y, at each occurrence, is C_{1-4}alkyl, C_{2-4}alkenyl, –OC_{1-4}alkyl, –OC_{1-4}haloalkyl, –OH, G^Y, –OG^Y, cyano, –SH, –SC_{1-4}alkyl, –SC_{1-4}haloalkyl, –SG^1, –NH_2, –NHC_{1-4}alkyl, –NHG^Y, –N(C_{1-4}alkyl)$_2$, –NHC(O)C_{1-4}alkyl, –NHC(O)OC_{1-4}alkyl, –C(O)C_{1-4}alkyl, –C(O)G^Y, –C(O)OG^Y, –C(O)OC_{1-4}alkyl, –C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –C(O)NHG^Y, –C(O)N(G^Y)$_2$, –SO_2C_{1-4}alkyl, –SO_2G^Y, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, or –$SO_2N(C_{1-4}alkyl)_2$; and

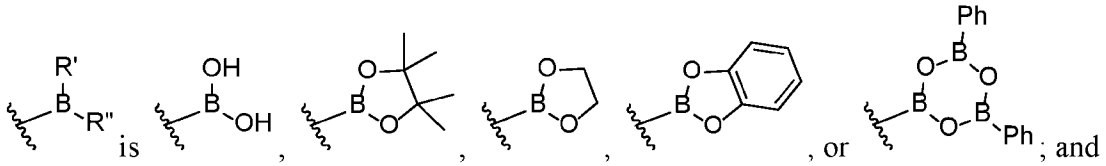
G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –$SO_2N(C_{1-4}alkyl)_2$;

the method comprising:

mixing a compound of formula (III):

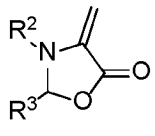


(III), wherein



is , , , , or ; and

a compound of formula (II),



(II),

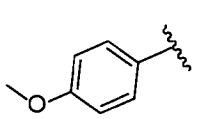
with a photocatalyst, a base, and D_2O to form a reaction mixture; and

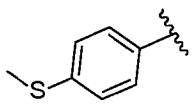
exposing the reaction mixture to light, thereby producing the deuterated compound of formula (I).

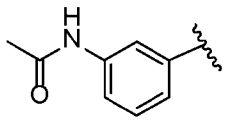
2. The method of claim 1, wherein R^1 is G^1.

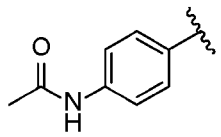
3. The method of claim 2, wherein G^1 is the optionally substituted 6- to 12-membered aryl.

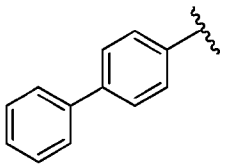
4. The method of claim 3, wherein the optionally substituted 6- to 12-membered aryl is optionally substituted phenyl.

5. The method of claim 4, wherein G^1 is 

, 

, 

, 

, or 
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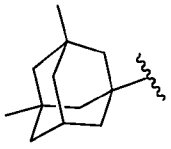
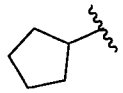
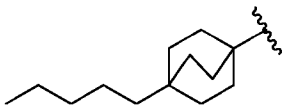
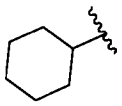
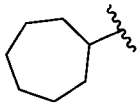
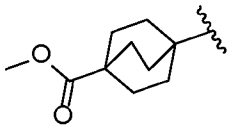
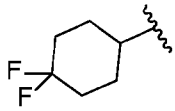
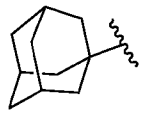
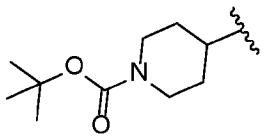
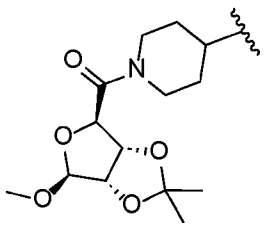
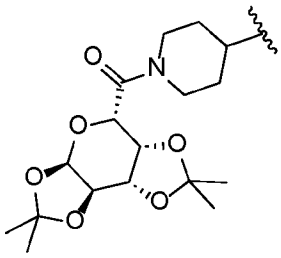
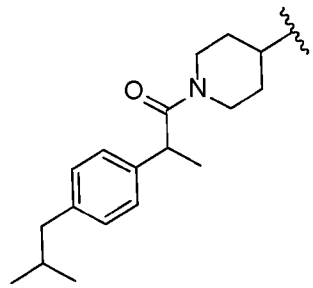
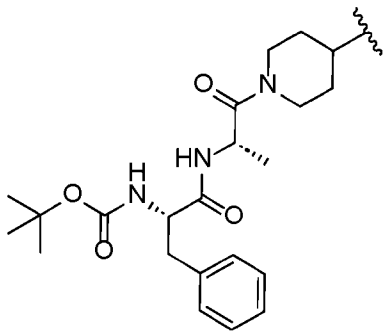
6. The method of claim 2, wherein G^1 is the optionally substituted C_{3-10}carbocyclyl.

7. The method of claim 6, wherein G^1 is  ,  ,  ,  ,  ,  ,  , or  .

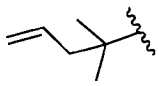
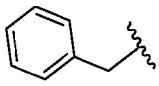
8. The method of claim 2, wherein G^1 is the optionally substituted 4- to 12-membered heterocyclyl.

9. The method of claim 8, wherein the optionally substituted 4- to 12-membered heterocyclyl is optionally substituted piperidinyl.

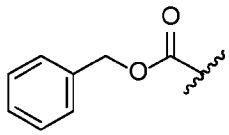
10. The method of claim 9, wherein G^1 is  ,  ,  ,  , or  .

11. The method of claim 1, wherein R^1 is $C_{1\text{-}10}$alkyl or $-L^1-R^Y$.

12. The method of claim 11, wherein R^1 is  or  .

13. The method of claim 11, wherein R^1 is  or  .

14. The method of claim 1, wherein R^2 is the amine protecting group.

15. The method of claim 14, wherein the amine protecting group is  (Cbz).

16. The method of claim 1, wherein R^2 is $C_{1\text{-}6}$alkyl.

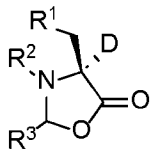
17. The method of claim 16, wherein R^2 is $-CH_3$.

18. The method of claim 17, wherein each hydrogen in the $-CH_3$ is deuterium.

19. The method of claim 1, wherein R^3 is $C_{1\text{-}6}$alkyl.

20. The method of claim 19, wherein R^3 is  .

21. The method of claim 1, wherein the compound of formula (I) is a compound of formula:



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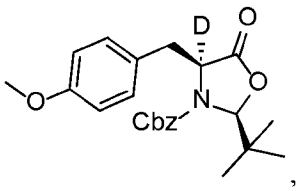
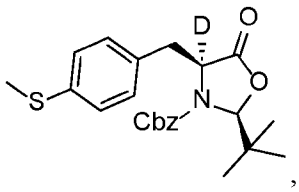
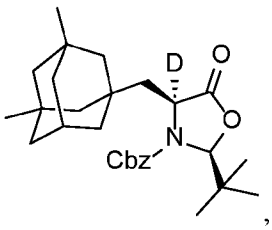
22. The method of claim 1, wherein the compound of formula (I) is



, 

, 

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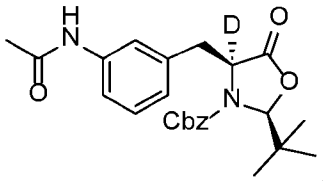
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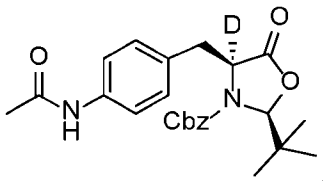
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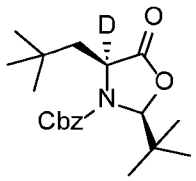
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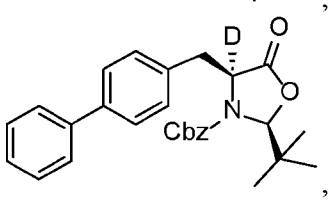
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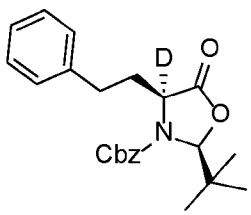
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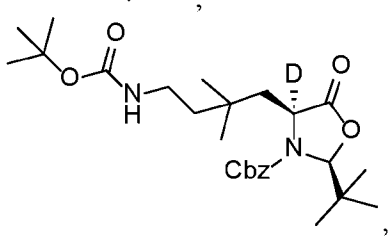
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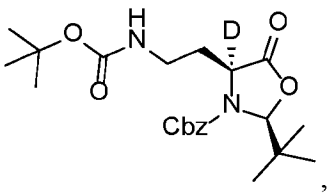
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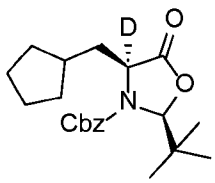
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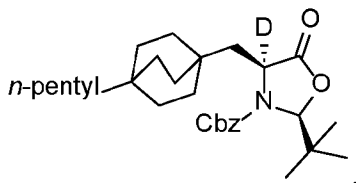
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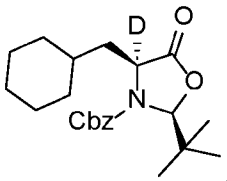
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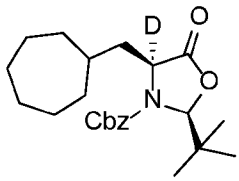
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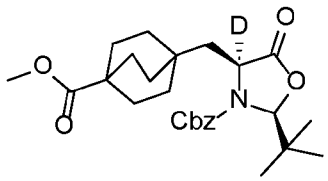
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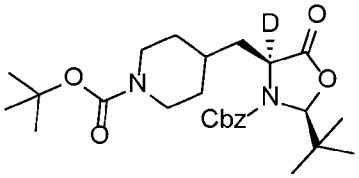
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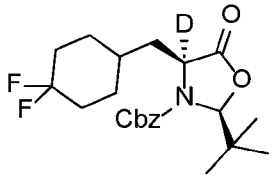
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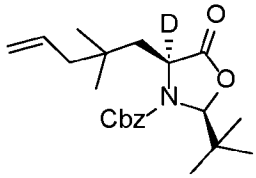
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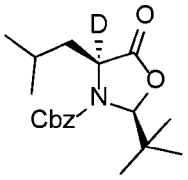
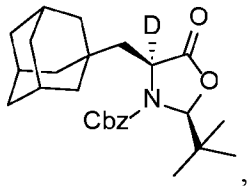
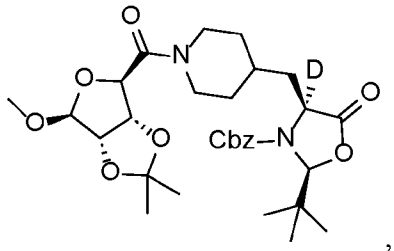
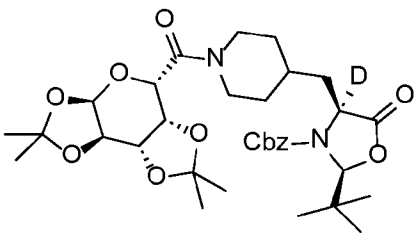
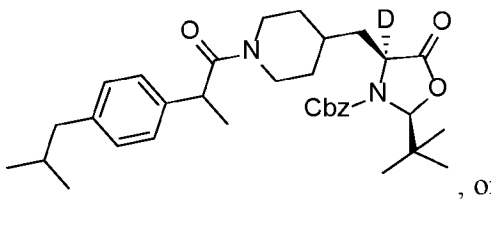
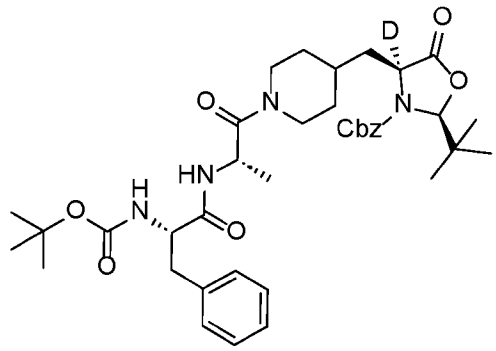
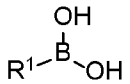

,

,

,

,

, or



23. The method of claim 1, wherein the compound of formula (I) has at least 75% deuterium incorporation at each deuterium label.

24. The method of claim 1, wherein the compound of formula (I) has at least 90% deuterium incorporation at each deuterium label.

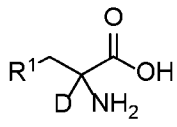
25. The method of claim 1, wherein the compound of formula (III) is  .

26. The method of claim 1, wherein the base is a Lewis base.

27. The method of claim 1, wherein the photocatalyst is an iridium (Ir)-based photocatalyst.

28. The method of claim 1, wherein the light is blue LED light.

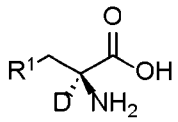
29. A method of preparing a deuterated compound of formula (I-AA), or a salt thereof,

 (I-AA),

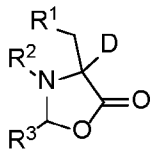
the method comprising:

preparing a deuterated compound of formula (I) according to the method of claim 1; then hydrolyzing the deuterated compound of formula (I).

30. The method of claim 29, wherein the deuterated compound of formula (I-AA) is



31. A deuterated compound of formula (I), or a salt thereof,


(I),

wherein:

R^1 is G^1, C_{1-10}alkyl, $-L^1-R^Y$, or $-G^1-L^1-R^Y$;

R^2 is an amine protecting group, hydrogen, or C_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{1-4}haloalkyl;

G^1, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^1 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, G^{1a}, –OH, $-OC_{1-6}$alkyl, $-OG^{1a}$, $-OC_{1-4}$haloalkyl, –SH, $-SC_{1-6}$alkyl, $-SG^{1a}$, $-SC_{1-4}$haloalkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-NHG^{1a}$, $-N(C_{1-4}alkyl)_2$, $-C(O)C_{1-4}$alkyl, $-C(O)G^{1a}$, $-C(O)OC_{1-4}$alkyl, $-C(O)OG^{1a}$, $-C(O)NH_2$, $-C(O)NHG^{1a}$, $-C(O)NHC_{1-4}$alkyl, $-C(O)N(C_{1-4}alkyl)_2$, $-SO_2C_{1-4}$alkyl, $-SO_2G^{1a}$, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, $-SO_2N(C_{1-4}alkyl)_2$, $-C_{1-4}$alkylene–OH, $-C_{1-4}$alkylene–OC_{1-4}alkyl, $-C_{1-4}$alkylene–NH_2, $-C_{1-4}$alkylene–NHC_{1-4}alkyl, $-C_{1-4}$alkylene–$N(C_{1-4}alkyl)_2$, –O–C_{1-4}alkylene–OH, –O–C_{1-4}alkylene–OC_{1-4}alkyl, –O–C_{1-4}alkylene–NH_2, –O–C_{1-4}alkylene–NHC_{1-4}alkyl, –O–C_{1-4}alkylene–$N(C_{1-4}alkyl)_2$, and C_{1-3}alkylene–G^{1a}, wherein G^1 is optionally further substituted with a peptide moiety comprising a chain of 1-8 amino acids, wherein each amino acid is optionally substituted with an amine protecting group and/or a carboxylic acid protecting group;

G^{1a}, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^{1a} is optionally substituted with 1-4 substituents independently selected from the group consisting

of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –SO_2N(C_{1-4}alkyl)$_2$;

L^1, at each occurrence, is a C_{1-10}alkylene, wherein optionally one or more methylene groups in the alkylene of L^1 are independently replaced with –O–, –S–, –SO–, –SO_2–, –C(O)–, –C(O)O–, –C(O)N(R^X)–, or –N(R^X)–, wherein 2 methylene groups replaced with –O–, –S–, –SO–, –C(O)O–, –C(O)N(R^X)–, –SO_2–, or –N(R^X)– are separated by two or more carbon atoms in the alkylene; and/or optionally one methylene group in the alkylene of L^1 is replaced with –Cy^1–;

Cy^1 is phenylene, C_{3-6}cycloalkylene, or a 4- to 6-membered heterocyclylene, wherein Cy^1 is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, and halogen;

R^X is hydrogen, C_{1-4}alkyl, C_{3-4}cycloalkyl, or –C_{1-3}alkylene–C_{3-4}cycloalkyl;

R^Y, at each occurrence, is C_{1-4}alkyl, C_{2-4}alkenyl, –OC_{1-4}alkyl, –OC_{1-4}haloalkyl, –OH, G^Y, –OG^Y, cyano, –SH, –SC_{1-4}alkyl, –SC_{1-4}haloalkyl, –SG^1, –NH_2, –NHC_{1-4}alkyl, –NHG^Y, –N(C_{1-4}alkyl)$_2$, –NHC(O)C_{1-4}alkyl, –NHC(O)OC_{1-4}alkyl, –C(O)C_{1-4}alkyl, –C(O)G^Y, –C(O)OG^Y, –C(O)OC_{1-4}alkyl, –C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –C(O)NHG^Y, –C(O)N(G^Y)$_2$, –SO_2C_{1-4}alkyl, –SO_2G^Y, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, or –SO_2N(C_{1-4}alkyl)$_2$; and

G^Y, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl, C_{3-10}carbocyclyl, or a 4- to 12-membered heterocyclyl, wherein G^Y is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-2}haloalkyl, halogen, cyano, –OH, –OC_{1-4}alkyl, –OC_{1-2}haloalkyl, –SH, –SC_{1-4}alkyl, –SC_{1-2}haloalkyl, –NH_2, –NHC_{1-4}alkyl, –N(C_{1-4}alkyl)$_2$, –C(O)C_{1-4}alkyl, –C(O)OC_{1-4}alkyl,–C(O)NH_2, –C(O)NHC_{1-4}alkyl, –C(O)N(C_{1-4}alkyl)$_2$, –SO_2C_{1-4}alkyl, –SO_2NH_2, –SO_2NHC_{1-4}alkyl, and –SO_2N(C_{1-4}alkyl)$_2$.

32. The compound of claim 31, or a salt thereof, wherein that compound has at least 50% deuterium incorporation at each deuterium label.

33. The compound of claim 31, or a salt thereof, wherein that compound has at least 75% deuterium incorporation at each deuterium label.

34. The compound of claim 31, or a salt thereof, wherein that compound has at least 90% deuterium incorporation at each deuterium label.

35. The compound of claim 31, or a salt thereof, wherein that compound has at least 95% deuterium incorporation at each deuterium label.

36. The compound of claim 31, or a salt thereof, wherein that compound has at least 99% deuterium incorporation at each deuterium label.

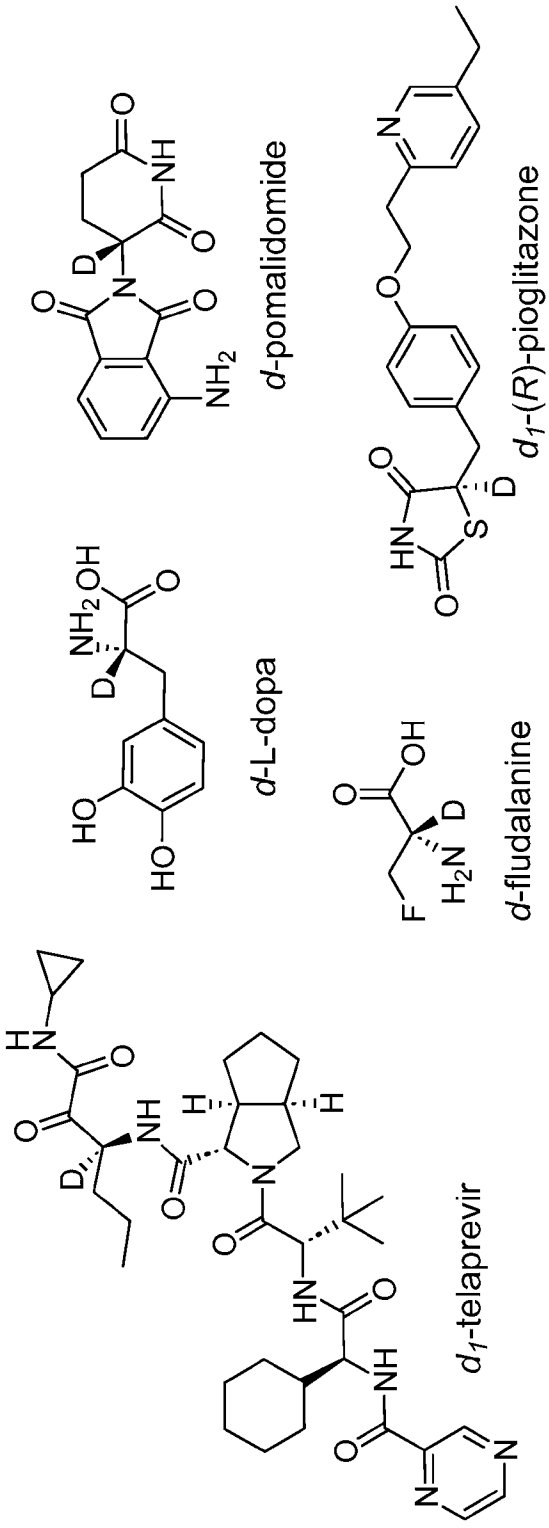
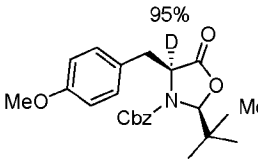
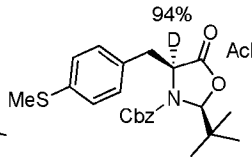

d-pomalidomide
d-L-dopa
d-fludalanine
d1-(R)-pioglitazone
d1-telaprevir

FIG. 1

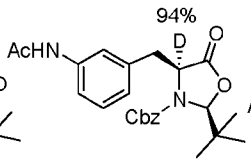
Aromatic Alkyl Radical:



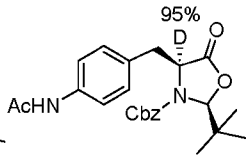
57%, dr >20:1
3a



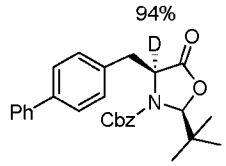
47%, dr >20:1
3b



54%, dr >20:1
3c

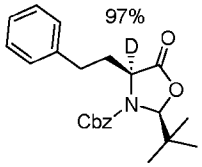


49%, dr >20:1
3d

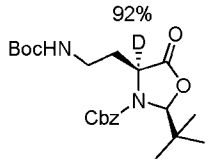


51%, dr >20:1,
0.3 equiv CsF used
3e

Primary Alkyl Radical:

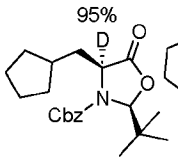


54%, dr >20:1
3f

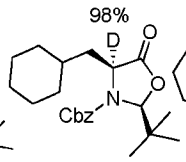


41%, dr >20:1
3g

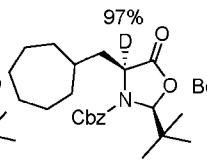
Secondary Alkyl Radical:



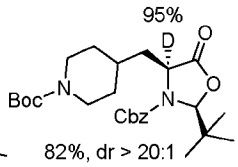
77%, dr > 20:1
3h



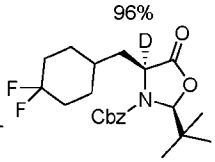
80%, dr > 20:1
3i



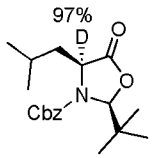
74%, dr > 20:1
3j



82%, dr > 20:1
81% in 1.5 mmol
scale, dr > 20:1
3k

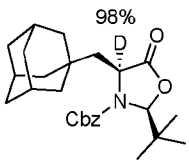


71%, dr > 20:1
3l

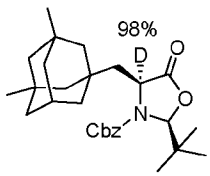


86%, dr > 20:1
3m

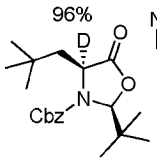
Tertiary Alkyl Radical:



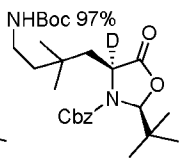
70%, dr > 20:1
3n



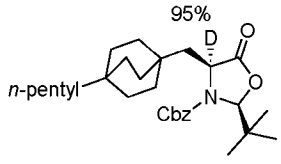
63%, dr > 20:1
3o



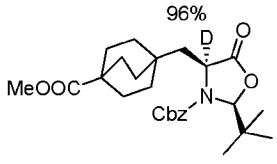
65%, dr > 20:1
3p



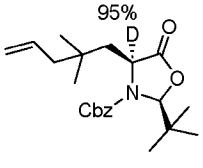
51%, dr > 20:1
3q



51%, dr > 20:1
3r



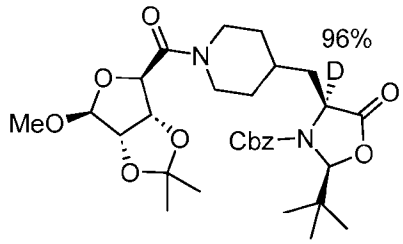
58%, dr > 20:1
3s



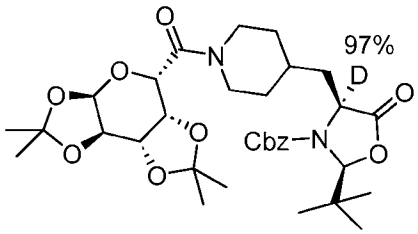
47%, dr > 20:1
3t

FIG. 2

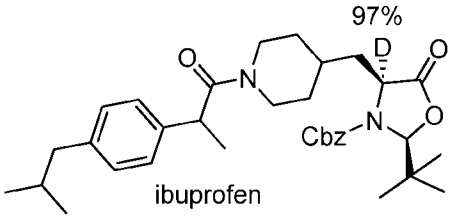
Late-stage functionalization of complex bioactive molecules:



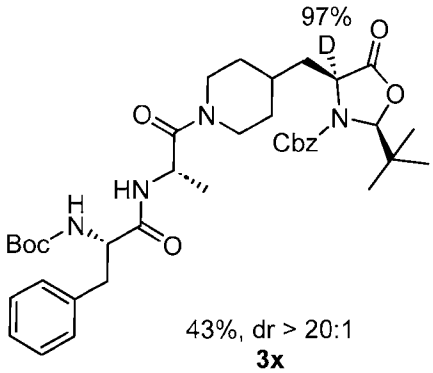
71%, dr > 20:1
3u



0.05M, 68%, dr > 20:1
3v



51%, dr > 20:1
3w



43%, dr > 20:1
3x

Converstion to a-deuterated L-Leu:

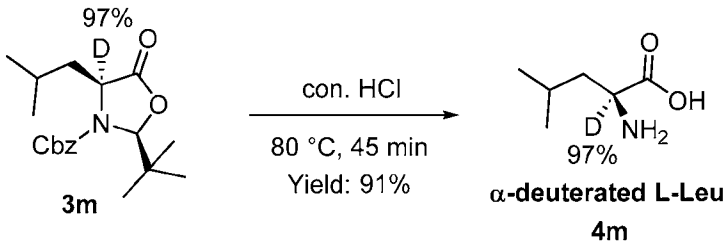


FIG. 3