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[54]	Title:	HETEROBICYCLIC COMPOUNDS AS BETA-LACTAMASE INHIBITORS		
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[57]	Abstract:	The present invention is directed to compounds which are beta-lactamase inhibitors. The compounds and their pharmaceutically acceptable salts, are useful in combination with beta-lactam antibiotics, or alone, for the treatment of bacterial infections, including infections caused by drug resistant organisms, including multi-drug resistant organisms. The present invention includes compounds according to formula (Ia): or a pharmaceutically acceptable salt thereof, wherein the values of R1, R2, R3 and R4 are described herein.		

HETEROBICYCLIC COMPOUNDS AS BETA-LACTAMASE INHIBITORS

Field of the Invention

The present invention relates to novel beta-lactamase inhibitors, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment of bacterial infections, including overcoming bacterial antibiotic resistance.

Background of the Invention

The international microbiological and infectious disease community continues to express serious concern that the continuing evolution of antibacterial resistance could result in bacterial strains against which currently available antibacterial agents will be ineffective. The outcome of such an occurrence could have considerable morbidity and mortality. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are typically regarded as having a broad spectrum of activity.

In the fight against bacterial infection, beta-lactam antibiotics are essential. Beta-lactams are a broad class of drugs which all have a beta-lactam in their core molecular structure, and typically show effectiveness against a broad spectrum of Gram-positive and Gram-negative bacteria by inhibiting the cell wall synthesis of the bacterium. Because the drug target has no eukaryotic analog, their toxicity is low and they are generally well-tolerated. They remain among the most widely prescribed, safe and effective drugs available to combat bacterial infection. However, their effectiveness is limited by highly resistant infectious strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant (MDR) strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli, Klebsiella pneumonia*, and other *Enterobacteriaceae*. Such resistant bacteria are major causes of patient morbidity and mortality. Helfand, *β-lactams Against Emerging 'Superbugs': Progress and Pitfalls*, Expert Rev. Clin. Pharmacol. 1(4):559-571 (2008).

Beta-lactam antibiotics, alone and in combination with beta-lactamase inhibitors, continue to

10/03/2014 08:46 0235

represent an essential portion of the antibacterial agents used to combat disease. β-lactam resistance for Gram-negative infections is primarily driven by β-lactamase activity; and the significant dependence on β-lacatam antibiotics has lead to the diversification and increased prevalence of β-lactamases. These β-lactamases are driving resistance to even the newest β-lactam antibiotics. Llarrull, et al., *The Future of Beta-Lactams*, Current Opinion in Microbiology, 13:551-557 (2010).

A major threat to the efficacy of these drugs is the increasing prevalence of extended-spectrum beta-lactamases (ESBLs). Beta-lactamases are enzymes that are secreted by some bacteria that ring open the beta-lactam portion of a beta-lactam antibiotic and thereby deactivate it. There are currently, four classes of beta-lactamases, denoted Class A, Class B, Class C and Class D. Class A, Class C and Class D beta-lactamases are serine beta-lactamase inhibitors, while Class B beta-lactamases are metallo-beta-lactamases (MBLs). Bush & Jacoby, *Updated Functional Classification of β-Lactamases*, Antimicrobial Agents and Chemotherapy, 54(3):969-976 (Mar. 2010).

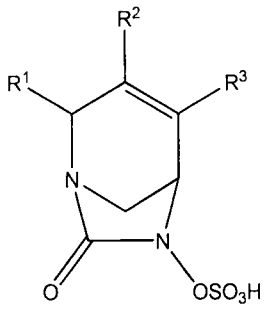
To help improve the effectiveness of beta-lactam antibiotics, some beta-lactamase inhibitors have been developed. However, the currently available β-lactamase inhibitors in many instances are insufficient to counter the constantly increasing diversity of β-lactamases. The three most common serine beta-lactamase agents currently used – clavulanic acid, tazobactam and sulbactam – have activity only against certain Class A enzymes, which severely limits their utility. Additionally, beta-lactamase inhibitors currently in clinical trials, such as Avibactam and MK7655 work primarily on Class A and C enzymes, with minimal effectiveness against Class D beta-lactamases. Bebrone, et al., *Current Challenges in Antimicrobial Chemotherapy: Focus on β-Lactamase Inhibition*, Drugs, 70(6):651-679 (2010). While these agents represent a considerable improvement over the currently available beta-lactamase inhibitors, agents which effectively hit all three serine beta-lactamases are desireable for combating the significant beta-lactam resistance seen today. Currently, there are no approved β-lactamase inhibitors which are effective against Class D β-lactamases, and resistance rates to conventional antibiotics are continuing to rise.

10/03/2014 08:43 0234

Therefore, there is a need for new β-lactamase inhibitors which are effective against at least D β-lactamases. There is a clear need for new β-lactamase inhibitors which are effective against more than one of Class A, C and/or D β-lactamases.

Summary of the Invention

The present invention is directed to compounds which are beta-lacatamase inhibitors. The compounds, and their pharmaceutically acceptable salts, are useful in combination with beta-lactam antibiotics, or alone, for the treatment of bacterial infections, including infections caused by drug resistant organisms, including multi-drug resistant organisms. More particularly, the invention relates to compounds of formula (Ia):



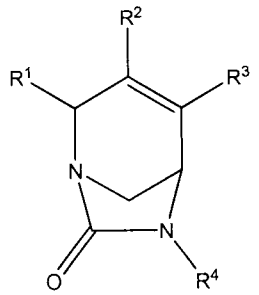
or a pharmaceutically acceptable salt thereof, wherein R^1 is –CONR'R'', -CN, or C_1-C_3 alkyl, wherein each alkyl is optionally substituted with C_1-C_3 alkoxy, -OH, –CN, -NR'R'', or -CONR'R''; R^2 and R^3 are independently selected from H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, -CONR'R'', or $C(O)_2R'$; wherein the alkyl, alkenyl, cycloalkyl, and alkoxy represented by R^2 or R^3 are independently and optionally substituted by one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', 5-7 membered heterocycle, -C(O)NR'R'' or -NR'C(O)R''; and each R' and R'' are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 5 to 6 membered heterocyclyl or a 5 to 6 membered heteroaryl; wherein each alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), $-NH_2$, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 5-7 membered heterocyclyl or a 5-7 membered heteroaryl; provided that R^2 and R^3 are not both hydrogen; and when R^1 is –C(O)NR'R'', then neither of R^2 or R^3 is –C(O)NR'R''.

10/03/2014 08:48 0255

10/03/2014 08:48 0266

Detailed Description of the Invention

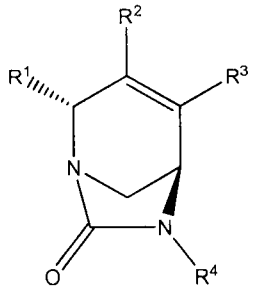
In one aspect of the invention is a beta-lactamase inhibitor compound according to formula (I):



or a pharmaceutically acceptable salt thereof, wherein R^1 is –CONR'R'', -CN, C_1-C_3 alkyl or C_1-C_2 alkoxy, wherein each alkyl and alkoxy is independently and optionally substituted with C_1-C_3 alkoxy, -OH, –CN, -NR'R'', –CONR'R'' or a 5-7 membered heterocycle; R^2 and R^3 are independently selected from H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, -CONR'R'', $C(O)_2R'$, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein the alkyl, alkenyl, cycloalkyl, alkoxy, phenyl, heterocyclyl and heteroaryl represented by R^2 or R^3 are independently and optionally substituted by one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', 5-7 membered heterocyclyl, -C(O)NR'R'' or -NR'C(O)R''; R^4 is $–OS(O)_2OH$, -$S(O)_2OH$, $-OP(O)_2OH$, $-P(O)_2OH$, $-C(O)NHS(O)_2R^5$, $-OCHFCO_2H$, $-OCF_2CO_2H$, or $-OCH_2CO_2H$; R^5 is NR'R'', phenyl, a 5-6 membered heterocyclyl or a 5 to 6 membered heteroaryl; and each R' and R'' is independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 5-7 membered heterocyclyl or a 5-6 membered heteroaryl; wherein each alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, $-C(O)(C_1$-C_6 alkyl), $-C(O)(C_1$-C_6 alkoxy), $-NH_2$, $-NH(C_1$-C_3 alkyl), $-N(C_1$-C_3 alkyl)$_2$, a 5-6 membered heterocyclyl or a 5-6 membered heteroaryl; or R' and R'' are taken together to form a 5-6 membered heterocyclyl or heteroaryl, wherein each heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, $-NH_2$, $-NH(C_1$-C_3 alkyl), or $-N(C_1$-C_3 alkyl)$_2$; provided that R^2 and R^3 are not both hydrogen; and when R^1 is –

C(O)NR'R'', then neither R^2 nor R^3 is –C(O)NR'R''.

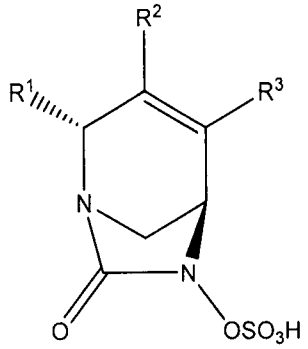
In another aspect of the invention is a compound according to formula (II):



(II)

or a pharmaceutically acceptable salt thereof wherein the variables R^1, R^2, R^3 and R^4 are as defined for formula (I) above.

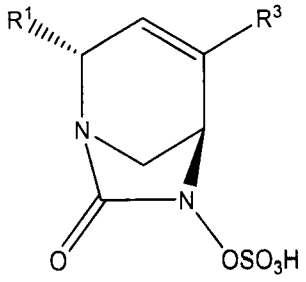
In one aspect of the invention is a compound according to formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein the variables R^1, R^2 and R^3 are as defined for formula (Ia) above.

In one aspect of the invention, is a compound according to formula (IV):



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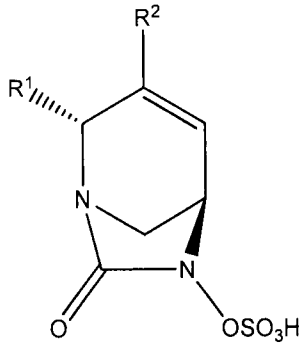
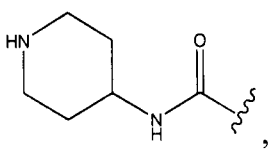
(IV)

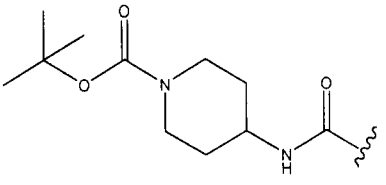
or a pharmaceutically acceptable salt thereof, wherein the variables R^1 and R^3 are as defined for fomula (Ia).

One aspect of the invention is a compound according to formula (V):



or a pharmaceutically acceptable salt thereof, wherein the variables R^1 and R^2 are as defined for formula (Ia).

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is -CONR'R'', -CN, or C_1-C_3 alkyl, wherein each alkyl is optionally substituted with C_1-C_3 alkoxy or -OH; and the R' and R'' of R^1 are independently selected from the group consisting of H, C_1-C_3 alkyl, or a 5-7 membered heterocyclyl , wherein each alkyl and heterocyclyl of R' and R'' is optionally and independently substituted with one or more -OH, C_1-C_3 alkyl, C_1-C_3 alkoxy, $-NH_2$, $-NH(C_1$-C_3 alkyl), $-N(C_1$-C_3 alkyl)$_2$, or a 5-7 membered heterocyclyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CH_2OCH_3$, -$CONH(CH_2)$-siderophore, $-CONH_2$, 

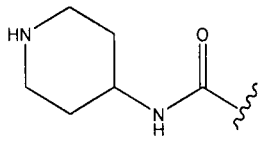
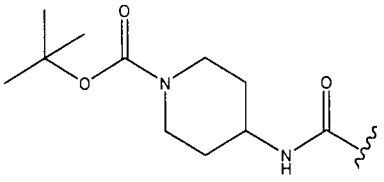
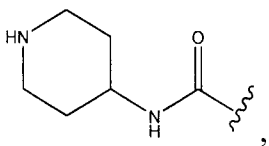
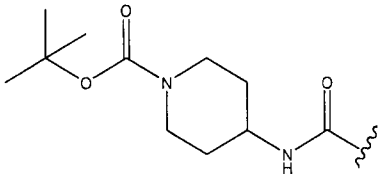
, or 

; and


represents the point of attachment to the bridged bicyclic core. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CH_2OCH_3$ or $-CONH_2$.

In one aspect of the invention, for any of formulae (I), (II), (III), or (IV), R^1 is $-C(O)NH_2$, -CN or C_1-C_3 alkyl optionally substituted with one or more –OH, C_1-C_3 alkoxy, halo, -OC(O)NR'R'', a

10/05/2014 08:48 0266

siderophore, or –C(O)NH(siderophore), wherein R' and R'' are as defined for any one of formulae (I), (Ia), (II), (III), (IV) or (V). In one aspect of the invention, for any one of formulae (I), (II), (III) or (IV), R^1 is $-C(O)NH_2$, -CN or C_1-C_2 alkyl optionally substituted with methoxy, -OH or -CN. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is -CONR'R'', $-CH_2OCH_3$ or -CN; and the R' and R'' of R^1 are independently -H, C_1-C_3 alkyl, or a 5-7 membered heterocyclyl, wherein each alkyl and heterocyclyl of R' and R'' is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, $-C(O)(C_1$-C_6 alkyl), $-C(O)(C_1$-C_6 alkoxy), $-NH_2$, $-NH(C_1$-C_3 alkyl), $-N(C_1$-C_3 alkyl)$_2$, or a 5-7 membered heterocyclyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CONH_2$, $-CONH(CH_2)_nNH_2$,  , or  ; n is an integer from 1 to 3; and  represents the point of attachment to the bridged bicyclic core. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CONH_2$,  , or  . In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CONH_2$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CH_2OCH_3$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is –CN. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CH_2OH$.

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, and -CONR'R'', wherein the alkyl and cycloalkyl represented by R^2 and/or R^3 are independently and optionally substituted by one or more group selected from halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', a siderophore, -C(O)NR'R'' and -NR'C(O)R''. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is methyl, ethyl, isopropyl, or

10/03/2014 08:45 0259

cyclopropyl, wherein each R^2 is optionally and independently substituted with one or more group selected from –OH and C_1-C_3 alkoxy. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is methyl.

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is -H, -CN, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, -CO_2R', -CONR'R'', or a 5-6 membered heterocyclyl, wherein each alkyl, cycloalkyl, heterocyclyl, R' and R'' of R^2 is optionally and independently subsituted with one or more group selected from halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, a siderophore, -C(O)NR'R'' and -NR'C(O)R''. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is H, -CN, methyl, ethyl, isopropyl, cyclopropyl, -CO_2(C_1-C_3 alkyl), -$CONH_2$, -CONH(C_1-C_3 alkyl), -CON(C_1-C_3 alkyl)$_2$, morpholinyl or thiazolyl, wherein when R^2 is not hydrogen or cyano, each R^2 is optionally and independently subsituted with one or more group selected from halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, a siderophore, -C(O)NR'R'' and -NR'C(O)R''. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is H, -CN, methyl, ethyl, propyl, isopropyl, thiazolyl, -CONR'R'', or -CO_2CH_3, wherein when R^2 is not hydrogen or cyano, each R^2 is optionally and independently substituted by one or more fluoro, chloro, bromo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy or -NR'R''; and R' and R'', when present in R^2, are independently selected from H and methyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (V), R^2 is H, -CN, methyl, isopropyl, –$CONHCH_3$, -CONH$(CH_2)_2NH_2$, -CO_2CH_3, -$(CH_2)NH_2$, -$(CH_2)_2NH_2$ or thiazolyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), or (III), R^2 is hydrogen.

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, and -CONR'R'', wherein the alkyl and cycloalkyl represented by R^2 and/or R^3 are independently and optionally substituted by one or more group selected from halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', a siderophore, -C(O)NR'R'' and -NR'C(O)R''. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_3-

C_6 cycloalkyl, or -CONR'R'', each of which is optionally and independently substituted with one or more substituent selected from the group consisting of halo, -CN, -OH, C_1-C_3 alkyl, cyclopropyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', a siderophore, -C(O)NR'R'' and -NR'C(O)R''; and each R' and R'' is independently selected from H and C_1-C_3 alkyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is methyl, ethyl, isopropyl, cyclopropyl, -$CONH_2$, -CONH(C_1-C_3 alkyl), or -CON(C_1-C_3 alkyl)$_2$, each of which is optionally and independently substituted with one or more group selected from -OH, C_1-C_3 alkyl, C_1-C_3 alkoxy, -NR'R'', C(O)NR'R'' and -NR'C(O)R''; and each R' and R'' is independently selected from H and C_1-C_3 alkyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is C_1-C_3 alkyl, cyclopropyl, –CONR'R'', wherein each alkyl, and cyclopropyl is optionally and independently substituted with one or more -OH, C_1-C_3 alkoxy, -NH_2, or -NHC(O)(C_1-C_3 alkyl); and each R' and R'' are independently selected from H, C_1-C_3 alkyl, and 5-6 membered heterocyclyl, wherein each alkyl and heterocyclyl represented by R' or R'' is optionally and independently substituted with one or more -OH, C_1-C_3 alkyl, or C_1-C_3 alkoxy. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is methyl, -CH_2OCH_3, or –$CONH_2$.

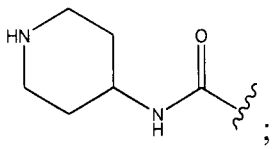
In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, -CO_2R', -CONR'R'', or a 5-6 membered heterocyclyl, each of which is optionally and independently subsituted with one or more group selected from halo, -CN, -OH, C_1-C_3 alkyl, cyclopropyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, -C(O)NR'R'' and -NR'C(O)R''; and wherein each R' and R'', when present in R^3, is independently selected from H and C_1-C_3 alkyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is H, methyl, ethyl, isopropyl, cyclopropyl, -CO_2(C_1-C_3 alkyl), -$CONH_2$, -CONH(C_1-C_3 alkyl), -CON(C_1-C_3 alkyl)$_2$, morpholinyl or thiazolyl, each of which is optionally and independently subsituted with one or more group selected from halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, cyclopropyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, -C(O)NR'R'' and -NR'C(O)R''; and wherein, when present in R^3, each R' and R'' is independently selected from H and C_1-C_3 alkyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is H, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl,

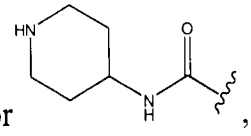
10/03/2014 08:40 027

-CONR'R'', or a heterocyclyl, wherein each alkyl, alkenyl, and heterocyclyl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), $-NH_2$, -NH(C_1-C_3 alkyl), or -N(C_1-C_3 alkyl)$_2$; and when present in R^3, each R' and R'' are optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, cyclopropyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), $-NH_2$, -NH(C_1-C_3 alkyl), or -N(C_1-C_3 alkyl)$_2$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is –CONR'R''; and one of R' and R'' is H and the other is C_1-C_3 alkyl optionally substituted with one or more halo, -CN, -OH, $-CF_3$, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, cyclopropyl, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), $-NH_2$, -NH(C_1-C_3 alkyl), or -N(C_1-C_3 alkyl)$_2$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is –CONH$(CH_2)_n$NHR'; R' is H, methyl, ethyl, propyl, isopropyl or cyclopropyl; and n is an integer from 1-3. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is –CONH$(CH_2)_2NH_2$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is methyl, isopropyl, isopropenyl, $-CONH_2$ or –CON$(CH_3)_2$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III) or (IV), R^3 is $-CH_2OCH_3$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), or (III), R^3 is hydrogen.

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 5 to 6 membered heterocyclyl or a 5 to 6 membered heteroaryl; wherein each alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), $-NH_2$, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 5-7 membered heterocyclyl or a 5-7 membered heteroaryl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' are independently selected from H, C_1-C_3 alkyl, and 5-6 membered heterocyclyl, wherein each alkyl and heterocyclyl represented by R' or R'' is optionally and independently substituted with one or more -OH, C_1-C_3 alkyl, or C_1-C_3 alkoxy. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' is independently selected from H and C_1-C_3 alkyl.

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' is independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 5-7 membered heterocyclyl or a 5-6 membered heteroaryl; wherein each alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), $-NH_2$, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 5-6 membered heterocyclyl or a 5-6 membered heteroaryl; or R' and R'' are taken together to form a 5-6 membered heterocyclyl or heteroaryl, wherein each heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, $-NH_2$, -NH(C_1-C_3 alkyl), or -N(C_1-C_3 alkyl)$_2$. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' is independently selected from hydrogen, and C_1-C_6 alkyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' is independently selected from hydrogen, methyl, ethyl, propyl and isopropyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' is independently selected from hydrogen and methyl. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), each R' and R'' is independently selected from an C_1-C_3 alkyl optionally substituted with one or more of methoxy, ethoxy, –OH, $-NH_2$, NH(CH_3), -N(CH_3)$_2$, or a siderophore. In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), one of R' and R'' is hydrogen, while the other is selected from any of the possible values listed above.

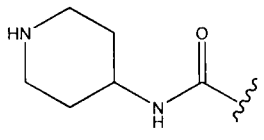
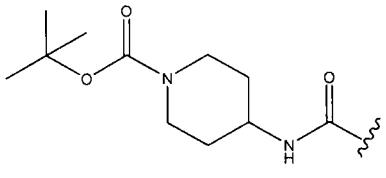
In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V), R^1 is $-CH_2OCH_3$; $-CONH_2$, or 

; R^2 is –H or $-CH_3$; and R^3 is –H, $-CH_3$, or $-CONH_2$; provided that R^2 and R^3 are not both H; and when R^1 is $-CONH_2$, or 

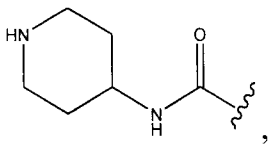
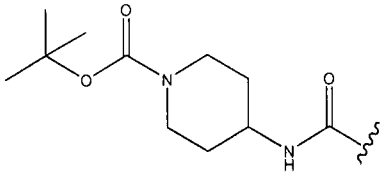
, then R^3 is not $-CONH_2$.

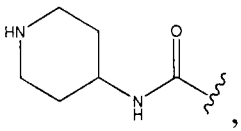
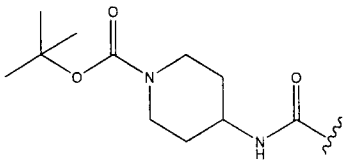
In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V),

19/03/2014 08:49 0274

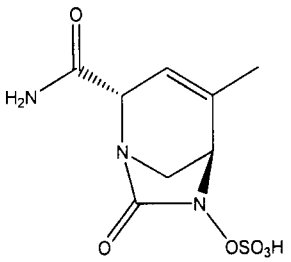
R^1 is $-CH_2OCH_3$; $-CONH_2$,  , or  ; R^2 is –H or methyl; R^3 is –H, $-CH_3$, or $-CONH_2$; and R^4 is $-OSO_2OH$.

In one aspect of the invention, for any one of formulae (I), (Ia), (II), (III), (IV) or (V),

R^1 is $-CH_2OCH_3$; –CONR'R'',  , or  ; R^2 is -H, C_1-C_3 alkyl or C_3-C_6 cycloalkyl; R^3 is –H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl or –CONR'R''; R^4 is $-OSO_2OH$; and each R' and R'' are independently –H or C_1-C_3 alkyl.

In either of the two above aspects of the invention, the compound is as defined, provided that R^2 and R^3 are not both H; and when R^1 is $-CONH_2$,  , or  ; then R^3 is not $-CONH_2$.

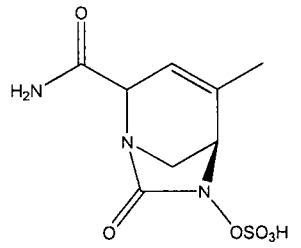
One aspect of the invention is the compound:



or a pharmaceutically acceptable salt thereof.

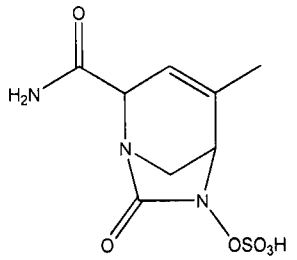
One aspect of the invention is the compound:

10/03/2014 08:42 0275



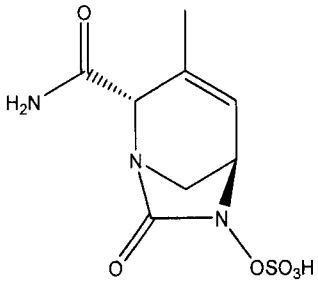
or a pharmaceutically acceptable salt thereof.

One aspect of the invention is the compound:



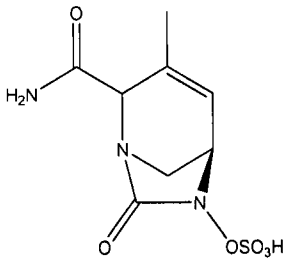
or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention is the compound:



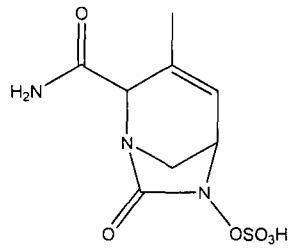
or a pharmaceutically acceptable salt thereof.

One aspect of the invention is the compound:



or a pharmaceutically acceptable salt thereof.

One aspect of the invention is the compound:



or a pharmaceutically acceptable salt thereof.

Any embodiment described herein can be combined with any other suitable embodiment described herein to provide additional embodiments. For example, where one embodiment individually or collectively describes possible groups for R^1 and a separate embodiment describeds possible groups for R^2, it is understood that these embodiments can be combined to provide an additional embodiment utilizing the possible groups for R^1 with the possible groups for R^2. Analogously, the invention encompasses any embodiments called out individually for R^1, R^2, R^3, R^4, R^5, R' and R'' in combination with any specific embodiments called out for each of the remaining variables.

Compounds of Formulae (I), (Ia), (II), (III), (IV) and (V) possess beneficial efficacious, metabolic, toxicological and/or pharmacodynamic properties.

In one aspect of the invention, the compound of formula (Ia) is selected from the group consisting of:

(2S,5R)-2-carbamoyl-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-2-cyano-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-4-methyl-7-oxo-2-(piperidinium-4-ylcarbamoyl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate;

(2S,5R)-2-carbamoyl-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-2-cyano-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

10/05/2014 09:48 0275

(2S,5R)-2-(2-aminoethylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate;

(2S,5R)-2-(methoxymethyl)-7-oxo-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-2-((5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)methylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-2-carbamoyl-4-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-2-carbamoyl-3-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sodium sulfate;

(2S,5R)-2-carbamoyl-3-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sodium sulfate;

(2S,5R)-4-carbamoyl-2-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate, monosodium salt;

(2S,5R)-2,4-bis(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate Sodium salt;

(2S,5R)-2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate sodium salt;

(2S,5R)-4-(dimethylcarbamoyl)-2-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate sodium salt;

(2S,5R)-2-(hydroxymethyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate Sodium Salt;

(2S,5R)-3-methyl-7-oxo-2-(piperidin-1-ium-4-ylcarbamoyl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate;

(2S,5R)-2-carbamoyl-3-(hydroxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-4-(2-amino-2-oxoethyl)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-4-carbamoyl-2-(hydroxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium Salt;

(2S,5R)-2-carbamoyl-3,4-dimethyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen

sulfate sodium salt;

(2S,5R)-2-carbamoyl-3-ethyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-4-(2-aminoethyl)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate;

(2S,5R)-2-carbamoyl-3-cyclopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-4-(2-acetamidoethyl)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate sodium salt;

(2S,5R)-2-(methoxymethyl)-4-(methylcarbamoyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-2-carbamoyl-4-cyclopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

(2S,5R)-3-(2-methoxyethyl)-2-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt; and

(2S,5R)-2-(((1,5-dihydroxy-4-oxo-1,4-dihydropyridin-2-yl)methyl)carbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt;

or a pharmaceutically acceptable salt thereof.

Alkyl - As used herein the term "alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. In one aspect, "alkyl" is methyl.

Alkenyl – As used herein, the term "alkenyl" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon double bond. For example, "C_{2-6}alkenyl" includes groups such as C_{2-5}alkenyl, C_{2-4}alkenyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, and 2-methyl-1-heptenyl.

Alkynyl – As used herein, the term "alkynyl" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon triple bond. For example, "C_{2-8}alkynyl" includes groups such as C_{2-6}alkynyl, C_{2-4}alkynyl, ethynyl, 2-propynyl, 2-methyl-2-propynyl, 3-butynyl, 4-pentynyl, 5-hexynyl, 2-heptynyl, and 4-methyl-5-heptynyl.

Halo – As used herein, the term "halo" is intended to include fluoro, chloro, bromo and iodo. In one aspect, the "halo" may refer fluoro, chloro, and bromo. In another aspect, "halo" may refer to fluoro and chloro. In still another aspect, "halo" may refer to fluoro. In yet another aspect, "halo" may refer to chloro.

Cycloalkyl - In one aspect, "cycloalkyl" refers to a saturated or partially saturated monocyclic carbon ring, of which one or more -CH_2- groups may be optionally replaced with a corresponding number of -C(O)- groups. Illustrative examples of "cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, and cyclopentenyl. In one aspect, "3- to 5-membered carbocyclyl" may be cyclopropyl.

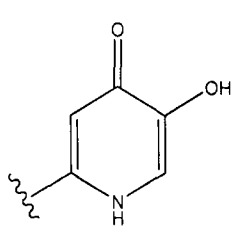
5-7 Membered Heterocyclyl - The term "5-7 membered heterocyclyl" refers to a saturated or partially saturated, non-aromatic monocyclic ring containing 5 to 7 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which a -CH_2- group may be optionally replaced by a -C(O)- group. Analogously, "5-6 membered heterocyclyl" refers to a saturated or partially saturated, non-aromatic monocyclic ring containing 5 to 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which a -CH_2- group may be optionally replaced by a -C(O)- group. Unless otherwise specified, "5-7 membered heterocyclyl" and "5-6 membered heterocyclyl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides or sulphones. Illustrative examples of "5-7 membered heterocyclyl" and "5-6 membered heterocyclyl" include, but are not limited to, azetidinyl, dioxidotetrahydrothiophenyl, 2,4-dioxoimidazolidinyl, 3,5-dioxopiperidinyl, furanyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, oxetanyl, oxoimidazolidinyl, 3-oxo-1-piperazinyl, 2-oxopyrrolidinyl, 2-oxotetrahydrofuranyl, oxo-1,3-thiazolidinyl, piperazinyl,

piperidyl, 2*H*-pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, 1,3,4-thiadiazolyl, thiazolidinyl, thiomorpholinyl, thiophenyl, 4*H*-1,2,4-triazolyl, pyridine-*N*-oxidyl, tetrazolyl, oxadiazolyl, triazolyl, pyrazinyl, triazinyl, and homopiperidinyl. In one embodiment, the terms "5-7membered heterocycylyl" and "5-6 membered heterocyclyl" includes siderophores of 5-7 or 5-6 members which contain at least one heteroatom.

5- or 6-Membered Heteroaryl –The term "5-6 membered heteroaryl" is refers to a monocyclic, aromatic heterocyclyl ring containing 5 or 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen. Unless otherwise specified, "5-6 membered heteroaryl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "5-6 membered heteroaryl" include furanyl, imidazolyl, isothiazolyl, isoxazole, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyridinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thiophenyl, and triazolyl.

6-Membered Heteroaryl – In one aspect, "heterocyclyl," 5- or 6-membered heterocyclyl," "6-membered heterocyclyl," and "5- or 6-membered heteroaryl" may be "6-membered heteroaryl." The term "6-membered heteroaryl" is intended to refer to a monocyclic, aromatic heterocyclyl ring containing 6 ring atoms. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Illustrative examples of "6-membered heteroaryl" include pyrazinyl, pyridazinyl, pyrimidinyl, and pyridinyl.

Siderophore – In one aspect, a "siderophore" is a low molecular weight moiety that can bind ferric iron. Once bound, these "iron carriers" can facilitate transport of the molecule into a bacterial cell. The term "siderophore" includes, but is not limited to the following heterocyclyls:



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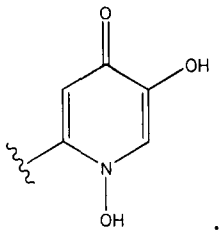

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Optionally substituted – As used herein, the phrase "optionally substituted" indicates that substitution is optional and therefore it is possible for the designated group to be either substituted or unsubstituted. In the event a substitution is desired, the appropriate number of hydrogens on the designated group may be replaced with a selection from the indicated substituents, provided that the normal valency of the atoms on a particular substituent is not exceeded, and that the substitution results in a stable compound.

In one aspect, when a particular group is designated as being optionally substituted with one or more substituents, the particular group may be unsubstituted. In another aspect, the particular group may bear one substituent. In another aspect, the particular substituent may bear two substituents. In still another aspect, the particular group may bear three substituents. In yet another aspect, the particular group may bear four substituents. In a further aspect, the particular group may bear one or two substituents. In still a further aspect, the particular group may be unsubstituted, or may bear one or two substituents.

Pharmaceutically Acceptable - As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Effective Amount – As used herein, the phrase "effective amount" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician.

Leaving Group – As used herein, the phrase "leaving group" is intended to refer to groups readily

19/03/2014 08:46 0034

displaceable by a nucleophile such as an amine nucleophile, and alcohol nucleophile, or a thiol nucleophile. Examples of suitable leaving groups include halo, such as fluoro, chloro, bromo, and sulfonyloxy group, such as methanesulfonyloxy and toluene-4-sulfonyloxy.

Protecting Group – As used herein, the term "protecting group" is intended to refer to those groups used to prevent selected reactive groups (such as carboxy, amino, hydroxy, and mercapto groups) from undergoing undesired reactions. Illustrative examples of suitable protecting groups for a hydroxy group include acyl groups; alkanoyl groups such as acetyl; aroyl groups, such as benzoyl; silyl groups, such as trimethylsilyl; and arylmethyl groups, such as benzyl. The deprotection conditions for the above hydroxy protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon. Illustrative examples of suitable protecting groups for an amino group include acyl groups; alkanoyl groups such as acetyl; alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, and *t*-butoxycarbonyl; arylmethoxycarbonyl groups, such as benzyloxycarbonyl; and aroyl groups, such benzoyl. The deprotection conditions for the above amino protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric, phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid, for example boron trichloride). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group, which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine. Another suitable protecting group for an amine is, for example, a cyclic ether such as tetrahydrofuran, which may

be removed by treatment with a suitable acid such as trifluoroacetic acid. The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or during work-up.

Compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) may form stable pharmaceutically acceptable acid or base salts, and in such cases administration of a compound as a salt may be appropriate. Examples of acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphorate, camphorsulfonate, choline, citrate, cyclohexyl sulfamate, diethylenediamine, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, meglumine, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, diphosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate. Examples of base salts include ammonium salts; alkali metal salts such as sodium, lithium and potassium salts; alkaline earth metal salts such as aluminum, calcium and magnesium salts; salts with organic bases such as dicyclohexylamine salts and N-methyl-D-glucamine; and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates such as dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; arylalkyl halides such as benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts may be useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

10/03/2014 09:46 0285

16/03/2014 08:45 0284

Compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) have one or more chiral centers, and it is to be understood that the invention encompasses all such stereoisomers, including enantiomers and diastereoisomers. Thus, it is to be understood that, insofar as certain of the compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The present invention encompasses all such stereoisomers having activity as herein defined.

The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Racemates may be separated into individual enantiomers using known procedures (see, for example, Advanced Organic Chemistry: 3rd Edition: author J March, p104-107). A suitable procedure involves formation of diastereomeric derivatives by reaction of the racemic material with a chiral auxiliary, followed by separation, for example by chromatography, of the diastereomers and then cleavage of the auxiliary species. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Thus, throughout the specification, where reference is made to the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), it is to be understood that the term compound includes isomers, mixtures of isomers, and stereoisomers that are β-lactamase inhibitors.

Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent.

When a specific stereoisomer is provided (whether provided by separation, by chiral synthesis, or by other methods) it is favorably provided substantially isolated from other stereoisomers of the same compound. In one aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) may contain less than 30%, particularly less than 20%, and more particularly less than 10% by weight of other stereoisomers of the same compound. In another aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) may contain less than 6%, particularly less than 3%, and more particularly less than 2% by weight of other stereoisomers of the compound. In another aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) may contain less than 1%, particularly less than 0.5%, and more particularly less than 0.3%, and still more particularly less 0.1% by weight of other stereoisomers of the compound.

It is to be understood that, insofar as certain of the compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) defined above may exist in tautomeric forms, the invention includes in its definition any such tautomeric form which possesses the above-mentioned activity. Thus, the invention relates to all tautomeric forms of the compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) whether explicitly detailed in the specification or not.

It is also to be understood that certain compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) and pharmaceutically salts thereof, can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms. For the sake of clarity, this includes both solvated (e.g., hydrated) forms of the free form of the compound, as well as solvated (e.g., hydrated) forms of the salt of the compound.

For the sake of clarity, it should be understood that the atoms of the compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) and of any of the examples or embodiments disclosed herein, are intended to encompass all isotopes of the atoms. For example, H (or hydrogen) includes any isotopic form of hydrogen including ^{1}H, ^{2}H (D), and ^{3}H (T); C includes any isotopic form of carbon including ^{12}C, ^{13}C, and ^{14}C; O includes any isotopic form of oxygen including ^{16}O, ^{17}O and ^{18}O; N includes any isotopic form of nitrogen including ^{13}N, ^{14}N and ^{15}N; P includes any isotopic form of phosphorous including ^{31}P and ^{32}P; S includes any isotopic form of sulfur

10/03/2014 08:45 0235

including ^{32}S and ^{35}S; F includes any isotopic form of fluorine including ^{19}F and ^{18}F; Cl includes any isotopic form of chlorine including ^{35}Cl, ^{37}Cl and ^{36}Cl; and the like. In one aspect, the compounds of Formulae (I), (Ia), (II), (III), (IV) or (V) include isotopes of the atoms covered therein in amounts corresponding to their naturally occurring abundance. However, in certain instances, it may be desirable to enrich one or more atom in a particular isotope which would normally be present in a lower abundance. For example, ^{1}H would normally be present in greater than 99.98% abundance; however, in one aspect, a compound of the invention may be enriched in ^{2}H or ^{3}H at one or more positions where H is present. In another aspect, when a compound of the invention is enriched in a radioactive isotope, for example ^{3}H and ^{14}C, the compound may be useful in drug and/or substrate tissue distribution assays. It is to be understood that the invention encompasses all such isotopic forms which are useful for treating bacterial infections.

In one aspect, the terms "infection" and "bacterial infection" may refer to a gynecological infection. In another aspect the terms "infection" and "bacterial infection" may refer to a respiratory tract infection (RTI). In still another, the terms "infection" and "bacterial infection" may refer to a sexually transmitted disease. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a urinary tract infection (UTI). In a further aspect, the terms "infection" and "bacterial infection" may refer to acute exacerbation of chronic bronchitis (ACEB). In yet a further aspect, the terms "infection" and "bacterial infection" may refer to acute otitis media. In one aspect, the terms "infection" and "bacterial infection" may refer to acute sinusitis. In another aspect, the terms "infection" and "bacterial infection" may refer to an infection caused by drug resistant bacteria. In still another aspect, the terms "infection" and "bacterial infection" may refer to catheter-related sepsis. In yet another aspect, the terms "infection" and "bacterial infection" may refer to chancroid. In a further aspect, the terms "infection" and "bacterial infection" may refer to chlamydia. In still a further aspect, the terms "infection" and "bacterial infection" may refer to community-acquired pneumonia (CAP). In yet a further aspect, the terms "infection" and "bacterial infection" may refer to complicated skin and skin structure infection. In one aspect, the terms "infection" and "bacterial infection" may refer to uncomplicated skin and skin structure infection. In another aspect, the terms "infection" and "bacterial infection" may refer to endocarditis. In still another aspect, the terms "infection" and "bacterial infection" may refer to febrile neutropenia. In yet another aspect, the terms "infection"

10/03/2014 08:45 0285

and "bacterial infection" may refer to gonococcal cervicitis. In a further aspect, the terms "infection" and "bacterial infection" may refer to gonococcal urethritis. In still a further aspect, the terms "infection" and "bacterial infection" may refer to hospital-acquired pneumonia (HAP). In yet another aspect, the terms "infection" and "bacterial infection" may refer to osteomyelitis. In a further aspect, the terms "infection" and "bacterial infection" may refer to sepsis. In still a further aspect, the terms "infection" and "bacterial infection" may refer to syphilis. In a further aspect, the terms "infection" and "bacterial infection" may refer to an intra-abdominal infection (IAI).

In one embodiment of the invention, the terms "infection" and "bacterial infection" refer to a infection caused by Gram-negative bacteria, also referred to as a "Gram-negative infection". In one aspect of this embodiment, the Gram-negative infection is a an infection resistant to one or more antibiotics. In one aspect of this embodiment, the Gram-negative infection is a multi-drug resistant infection.

All the above mentioned infections can be caused by a variety of bacteria that potentially could be treatable with the claimed agents in combination with penicillin-binding protein inhibitors, or by itself. In one embodiment of the invention is a method of treating one or more of the infections listed above comprising administering to a subject suffering from a bacterial infection an effective amount of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) or a pharmaceutically acceptable salt thereof, in combination with an additional antibiotic agent. In one aspect of this embodiment, the additional antibiotic agent is a β-lactam antibiotic. In one aspect of this embodiment, the additional antibiotic agent is a penicillin-binding protein inhibitor.

In one aspect, there is provided the use of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the production of a bacterial peptidoglycan inhibitory effect, either alone or in combination with a penicillin-binding protein inhibitor, in a warm-blooded animal such as man.

In another aspect, there is provided the use a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the

10/03/2014 08:48 0287

treatment of a bacterial infection in a warm-blooded animal such as man. In one aspect, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, is administered in combination with an additional antibiotic agent, such as a β-lactam antibiotic. In one aspect of this embodiment, the additional antibiotic agent is a penicillin-binding protein inhibitor.

In still another aspect, there is provided the use of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of urinary tract infections, pneumonia, prostatitis, skin and soft tissue infections, sepsis, and intra-abdominal infections, in a warm-blooded animal such as man. In one aspect of this embodiment, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is administered in combination with an additional antibiotic agent. In one aspect of this embodiment, the additional antibiotic agent is a penicillin-binding protein inhibitor.

In another aspect, there is provided a method for producing a bacterial peptidoglycan inhibitory effect, either alone or in combination with a penicillin-binding protein inhibitor, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof.

In a further aspect, there is provided a method for treating a bacterial infection in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, is administered in combination with an additional antibiotic agent. In one aspect of this embodiment, the additional antibiotic agent is a penicillin-binding protein inhibitor. In one aspect, the additional antibiotic agent is a β-lactam antibiotic.

In still a further aspect, there is provided a method for treating urinary tract infections, pneumonia, prostatitis, skin and soft tissue infections, sepsis, and intra-abdominal infections, in a

10/03/2014 08:40 0233

warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, is administered in combination with an additional antibiotic agent. In one aspect of this embodiment, the additional antibiotic agent is a penicillin-binding protein inhibitor. In one aspect, the additional antibiotic agent is a β-lactam antibiotic.

In yet a further aspect, there is provided a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in producing a bacterial peptidoglycan inhibitory effect, either alone or in combination with a penicillin-binding protein inhibitor, in a warm-blooded animal such as man. In one aspect, there is provided a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in treating Gram-negative bacterial infections, either alone or in combination with a beta-lactam antibiotic.

In one aspect of the invention, there is provided a method of inhibiting one or more beta-lactamase enzyme comprising administering a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, to an animal in need thereof. In a further aspect, the one or more beta-lactamase enzyme is a serine beta-lactamase enzyme. In a further asepct, the one or more beta-lactamase enzyme is selected from the group consisting of Class A, Class C and Class D. In a further asepct, the one or more beta-lactamase enzyme is a Class A enzyme. In a further asepct, the one or more beta-lactamase enzyme is a Class C enzyme. In a further asepct, the one or more beta-lactamase enzyme is a Class D enzyme. In a further aspect, the one or more beta-lactamase enzyme is a Class D enzyme and one or more of Class A and C enzymes.

The beta-lactamase inhibitors of Formulae (I), (Ia), (II), (III), (IV) or (V) can be administered in combination with any β-lactam antibiotic belonging, but not limited to, the classes of clavams, carbapenems, monobactams, penicllins, and or cephalosporins, or with any other compound susceptible to serine β-lactamases. In one aspect of the invention, a compound of formula (I), (Ia), (II), (III), (IV) or (V) is combined with one or more of: penicillin, methicillin, oxacillin,

10/23/2014 08:46 0289

nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalexin, cephalothin, CXA-101, cefazolin, cefaclor, cefuroxime, cefamandole, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, ceftobiprole medocaril, cefepime, cefpirome, ceftaroline, imipenem, meropenem, ertapenem, faropenem, sulopenem, doripenem, PZ-601 (Protez Pharmaceuticals), ME1036 (Forest Labs), BAL30072, MC-1, tomopenem, tebipenemn, aztreonam, tigemonam, nocardicin A, or tabtoxinine-β-lactam. In one aspect of the invention, a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is combined with meropenem, aztreonam, or ceftazidime. In one aspect of the invention, a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is combined with meropenem. In one aspect of the invention, a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is combined with aztreonam. In one aspect of the invention, a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is combined with ceftazidime. In one aspect of the invention, a compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is combined with ceftaroline fosamil.

In another aspect of the invention, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is administered in combination with a β-lactam antibiotic and an additional antibiotic and/or an additional β-lactamase inhibitor. In one aspect of the invention, the additional antibiotic agent is selected from one of the classes of aminoglycosides, spectinomycins, macrolides, ketolides, streptogramins, oxazolidinones, tetracyclines, fluoroquinolones, coumarin antibiotics, glycopeptides, lipoglycopeptides, nitroimidazoles, ansamycins, phenicols, mupirocyn, fosfomycin, tobramycin, linezolid, daptomycin, vancomycin, and the clasess mentioned in ANTIMICROBIAL AGENTS (ASM Press, Ed: A. Bryskier (2005)).

In one aspect of the invention, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is administered in combination with a β-lactam antibiotic and a second agent which is designed to address β-lactam resistance. In one aspect of the invention, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V) is administered in combination with a β-lactam antibiotic and a second serine beta-lactamase inhibitor. In one aspect of the invention, the second beta-lactamase inhibitor is selected from sulbactam, tazobactam, avibactam, clavulanic acid, LK-157, LK-176, SA-1-204, SA-2-13, BLI-489 (Pfizer/Wyeth), BAL0029880 and MK7655. In another aspect of

19/03/2014 COPY 46 0259

the invention, the second agent designed to address β-lactam resistance may be a metallo-beta-lactamase (MBL) inhibitor, also known as a Class B inhibitor.

In one aspect, there is provided a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in treating a bacterial infection in a warm-blooded animal, such as man.

In another aspect, there is provided a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in treating urinary tract infections, pneumonia, prostatitis, skin and soft tissue infections, sepsis and intra-abdominal infections, in a warm-blooded animal such as man.

In still another aspect, there is provided a pharmaceutical composition comprising a compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). In one aspect of the invention, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, is administered intravenously. In another aspect of the invention, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, is administered intravenously in combination with one or more other antibacterial agent. In one aspect of this embodiment, the compound of Formulae (I), (Ia), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, is administered simultaneously with one or more other antibacterial agents.

10/03/2014 08:45 0251

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate; granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl *p*-hydroxybenzoate; and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form or in the form of nano or micronized particles together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

10/03/2014 09:46 0252

condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives such as ethyl or propyl p-hydroxybenzoate; anti-oxidants such as ascorbic acid); coloring agents; flavoring agents; and/or sweetening agents such as sucrose, saccharine or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as arachis oil, olive oil, sesame oil or coconut oil or in a mineral oil such as liquid paraffin. The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

10/03/2014 08:48 0293

10/03/2014 08:46 0254

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 4 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 1000 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful classes of antibacterial agents (for example, macrolides, quinolones, ß-lactams or aminoglycosides) and/or other anti-infective

agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient.

In addition to its use in therapeutic medicine, the compound of Formulae (I), (II), (III) or (IV) and its pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of DNA gyrase in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Compounds of Formula (I), (Ia), (II), (III), (IV) or (V) may be prepared in a variety of ways. The processes shown below illustrates a method for synthesizing compounds of Formula (Ia) (wherein $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^3}$ unless otherwise defined, are as defined hereinabove). The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must then be used. The Schemes and Processes are not intended to present an exhaustive list of methods for preparing the

compounds of Formulae (I), (Ia), (II), (III), (IV) or (V); rather, additional techniques of which the skilled chemist is aware may be also be used for the compounds' synthesis. The claims are not intended to be limited to the structures shown in the Schemes and Processes.

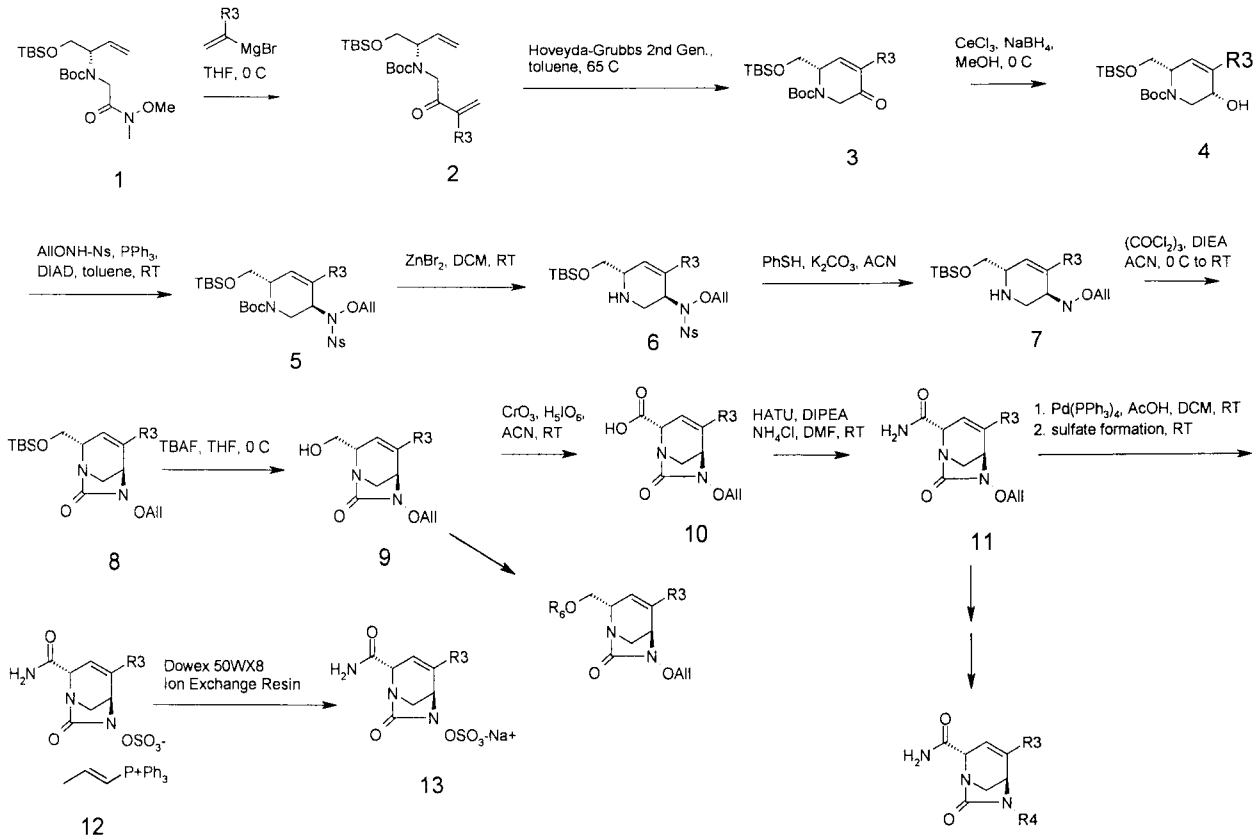
It will also be appreciated that in some of the reactions shown in the the Schemes and Processes mentioned herein, it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, *Protective Groups in Organic Synthesis*, published by John Wiley and Sons, (1991)) and as described hereinabove.

The skilled chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples and Scheme herein, to obtain necessary starting materials and products.

If not commercially available, the necessary starting materials for the procedures such as those described herein may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the described procedure or the procedures described in the Examples.

It is noted that many of the starting materials for synthetic methods as described herein are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to *Advanced Organic Chemistry*, 5th Edition, by Jerry March and Michael Smith, published by John Wiley & Sons (2001), for general guidance on reaction conditions and reagents.

SCHEME 1:



In one aspect, compounds of Formulae (I), (Ia), (II), (III), (IV) or (V), or pharmaceutically acceptable salts thereof, may be prepared by the process outlined in Scheme 1. From the Weinreb amide, compound 1, introduction of substituents at the R^3 position of Formula (I), (Ia), (II), (III), (IV) or (V) may be done via a Grignard reaction, followed by the rest of the synthetic steps shown above to yield final compounds. Compounds with different substituents at the R^4 position can be synthesized from compound 11 by N-O reduction and deallylation followed by subsequent reaction with the amine, such as alkylation or reaction with a substituted sulphone or a substituted isocyanate. Similarly, compounds with $R^1 = CH_2OR$, can be made from intermediate 9, using standard alkylation techniques.

An alternative means of synthesizing compounds with substitutents at R^3 utilizes the Baylis-Hillman product of enone followed by standard functional group transformations showing below, wherein the hydroxide group can be transformed into a leaving group, Q, which can subsequently be displaced by an appropriate nucleophile.

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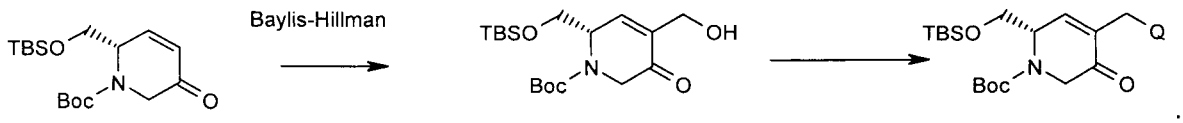
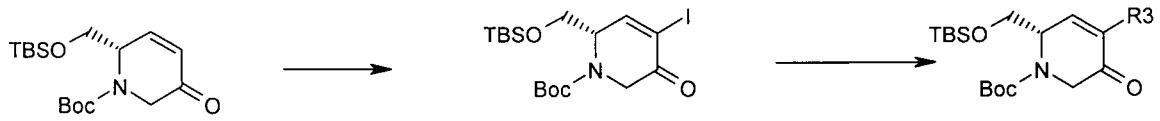
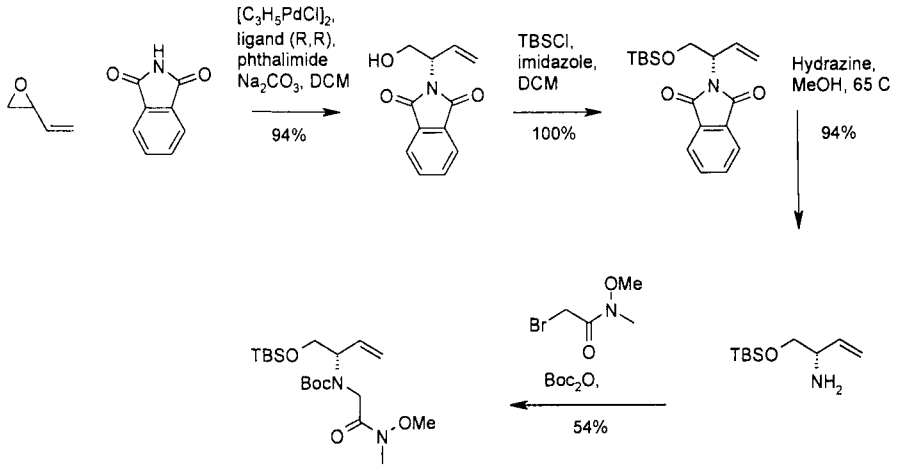


Others R^3 analogs can be made through cross-coupling of corresponding halide enone, as shown below.

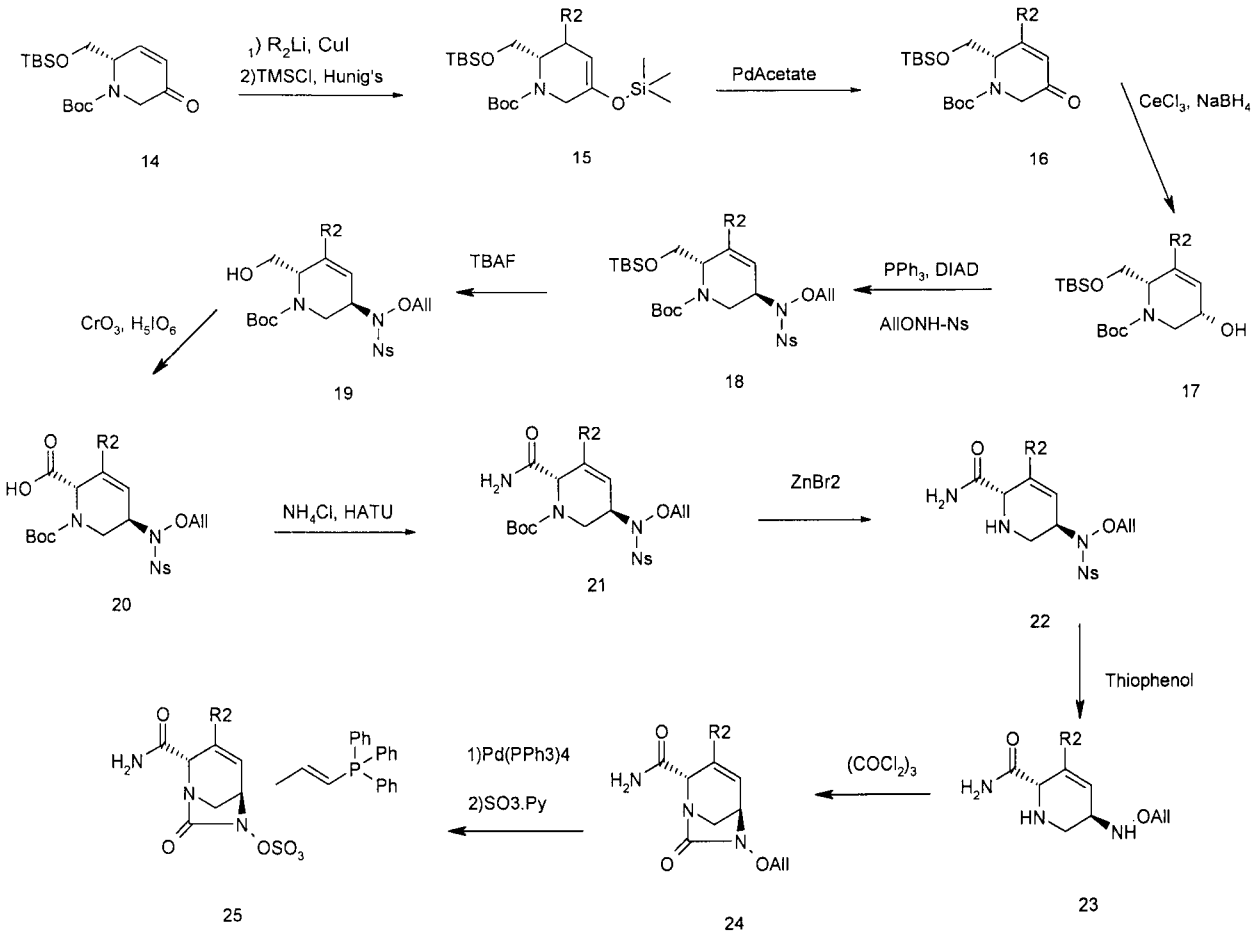


The Weinreb amide, compound 1, can be made easitly prepared from corresponding amine by through alkylation, as shown below.



Compounds with substitution at R^2 can be installed via Michael Addition, according to Scheme 2 below:

SCHEME 2



In any of the above-mentioned pharmaceutical compositions, processes, methods, uses, medicaments, and manufacturing features of the instant invention, any of the alternate embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be further described with reference to the following illustrative examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations are carried out at room temperature or ambient temperature, that is, in a range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of organic solvent was carried out using a rotary evaporator under reduced pressure (4.5 – 30 mmHg) with a bath temperature of up to 60 °C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography

(TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC or liquid chromatography/mass spectroscopy (LC/MS) and reaction times are given for illustration only;

(v) final products have satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectra data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz in DMSO-d_6 unless otherwise stated;

(viii) chemical symbols have their usual meanings;

(ix) solvent ratio was given in volume : volume (v/v) terms;

(x) an ISCO Combiflash refers to flash chromatography on silica gel using Isco Combiflash® separation system: RediSep normal phase flash column, flow rate, 30-40 ml/min;

(xi) the following abbreviations may have been used:

ACN	Acetonitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Boc_2O	*tert*-butyloxycarbonyl anhydride
DAST	Diethylaminosulfur trifluoride
DCM	dichloromethane
DIPEA/DIEA	*N, N*-diisopropylethylamine
DMAc	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EtOAc/EA	ethyl acetate
Et_2O	diethyl ether

10/03/2014 08:46 0320

GC	gas chromatography
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
Hex	hexanes
HPLC	high-performance liquid chromatography
hr/h	hours
LDA	Lithium diisopropylamide
MeCN	acetonitrile
MeOH	methanol
mins/min	minutes
o/n	overnight
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
*i*PrOH	*i*-propanol
rac.	racemic
TBAF	tetra-n-butylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethyl silyl
Tosyl, Ts	para-toluenesulfonyl

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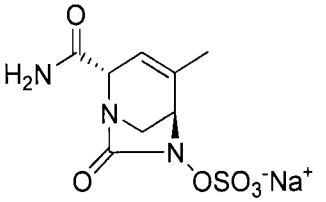
EXAMPLE 1

(2S,5R)-2-carbamoyl-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt



Dowex(R) 50WX8-100, ion-exchange resin (39 g) was conditioned by stirring for 3 hours in 2N sodium hydroxide (95 mL). The resin was then loaded into a cartridge and washed with water until pH 7. It was then washed with (1/1) acetone/water, followed by water again. (E)-

triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 17**, 0.2997 g, 0.52 mmol) was taken up in acetone and diluted with water. The solution was loaded on the resin and eluted with water. The fractions containing desired product were combined and lyophilized. The desired product was obtained as a light yellow solid (140 mg, 90%).

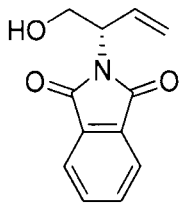
Optical rotation: (0.1 g/dL, MeOH) = -219

MS: 278 ES+ ($C_8H_{11}N_3O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.78 (m, 3H); 3.20 (m, 2H); 3.96 (m, 1H); 4.11 (m, 1H); 5.42 (m, 1H); 7.25 (bs, 1H); 7.51 (bs, 1H).

Route 1

Intermediate 1: (S)-2-(1-hydroxybut-3-en-2-yl)isoindoline-1,3-dione



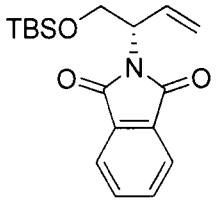
A 2-L reaction flask containing a stir bar and sodium carbonate (1.981 g, 18.69 mmol) was placed under high vacuum and dried with a heating gun for ten minutes. Upon cooling, the flask was backfilled with nitrogen. To it was added allylpalladium chloride dimer (0.553 g, 1.53 mmol), (1R,2R)-(+)-1,2-diaminocyclohexane-N,N'-bis(2-diphenylphosphino-1-naphthoyl) (CAS 174810-09-4)(3.36 g, 4.25 mmol), and phthalimide (50 g, 339.83 mmol). The flask was then purged with nitrogen for ten minutes. 1.4 L methylene chloride, previously degassed with a nitrogen line for ten minutes, was then added. This suspension was placed under an atmosphere of nitrogen; it was alternately stirred and sonicated over a ten-minute period to facilitate solvation. At that time it was a yellow or light orange solution containing white solid.To this mixture was added 2-vinyloxirane (24.06 g, 343.23 mmol). The resulting mixture was stirred under a nitrogen atmosphere at ambient temperature for approximately 48 hours. Analysis during that time by LCMS and TLC (1:1 hexanes:ethyl acetate) suggested progression of the reaction, and final analyses by those methods suggested complete conversion of starting material to one

major product. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The yellow, viscous fluid was injected onto a 330-g silica column: a minimal volume of methylene chloride was used to thin the crude material. Silica gel chromatography (15-75% ethyl acetate in hexanes, 40 minutes, 330-g column) was used to isolate the desired product as a viscous yellow fluid that became a pale yellowish white solid (69.6 g, 94%) over a period of hours under reduced pressure.

Optical Rotation : (2.02 g / 100 mL, methylene chloride) literature value = -72.2, obtained value = -71.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.66 (ddd, J=11.00, 6.47, 5.76 Hz, 1 H) 3.97 (ddd, J=10.95, 9.63, 5.67 Hz, 1 H) 4.69 - 4.79 (m, 1 H) 5.01 (dd, J=6.52, 5.76 Hz, 1 H) 5.18 (dt, J=2.79, 1.35 Hz, 1 H) 5.23 (dt, J=9.44, 1.42 Hz, 1 H) 6.07 (ddd, J=17.28, 10.67, 6.42 Hz, 1 H) 7.86 (q, J=1.83 Hz, 4 H)

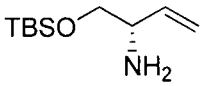
Intermediate 2: (S)-2-(1-(tert-butyldimethylsilyloxy)but-3-en-2-yl)isoindoline-1,3-dione



To a stirred solution of (S)-2-(1-hydroxybut-3-en-2-yl)isoindoline-1,3-dione (**Intermediate 1**, 69.4 g, 319.49 mmol) and imidazole (26.1 g, 383.39 mmol) in methylene chloride (160 mL), at ambient temperature under an atmosphere of nitrogen, was added tert-butyldimethylchlorosilane (55.4 g, 367.41 mmol) as a solid. This addition was performed over approximately ten minutes. Warming of the mixture was observed during this addition. After two hours stirring, the solution was poured into a saturated solution of aqueous sodium bicarbonate (approximately 150 mL); this biphasic mixture was shaken, and the organic layer was separated. The aqueous layer was back-extracted three times with 200 mL methylene chloride each time. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. The desired product was obtained as a pale yellow solid after drying overnight under high vacuum (107 g, 101%).

^{1}H NMR (300 MHz, DMSO-d_6) δ: -0.13 (s, 3 H) -0.04 (s, 3 H) 0.67 (s, 9 H) 3.85 (dd, J=10.20, 5.85 Hz, 1 H) 4.08 (t, J=10.01 Hz, 1 H) 4.76 - 4.86 (m, 1 H) 5.20 - 5.33 (m, 1 H) 5.25 (dt, J=2.79, 1.35 Hz, 1 H) 6.08 (ddd, J=17.23, 10.53, 6.42 Hz, 1 H) 7.86 (dq, J=4.51, 2.21 Hz, 4 H).

Intermediate 3: (S)-1-(tert-butyldimethylsilyloxy)but-3-en-2-amine



To a stirred solution of (S)-2-(1-(tert-butyldimethylsilyloxy)but-3-en-2-yl)isoindoline-1,3-dione (**Intermediate 2**, 108.28 g, 326.65 mmol) in methanol (1000 ml), at ambient temperature under a nitrogen atmosphere, was added hydrazine (35.9 ml, 1143.29 mmol). The yellow solution was heated to 65 °C. Within 30 minutes of reaching reaction temperature, a white precipitate was observed in the reaction mixture; this solid quickly became the bulk of the mixture, and at that time water (about 150 mL) was added to the reaction mixture. The reaction continued stirring without interruption and within a few minutes the solid dissolved. Upon complete conversion as indicated by LCMS analysis (both starting material and product give strong UV signals and are easily identified by LCMS), the heat was removed and more water was added (a total water content of 600 mL). The mixture was allowed to come to ambient temperature.
The methanol was removed in vacuo at 35 °C (moderately reduced pressure); vacuum was removed and the aqueous was warmed to about 50 °C and then extracted with 4 x 200-mL methylene chloride. This approach can lead to difficulty in separation of water from organic, so plenty of brine should be used as the last step of the workup. The organic extracts were combined, washed with saturated sodium bicarbonate (aq), washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo at not more than 30 °C. The desired product was obtained as a yellow liquid (58.5 g, 94%).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.03 (s, 6 H) 0.86 (s, 9 H) 1.51 (br. s., 2 H) 3.22 - 3.30 (m, 1 H) 3.33 - 3.48 (m, 2 H) 4.98 - 5.05 (m, 1 H) 5.17 (dt, J=17.28, 1.84 Hz, 1 H) 5.79 (ddd, J=17.37, 10.39, 5.67 Hz, 1 H).

Intermediate 4: 2-bromo-N-methoxy-N-methylacetamide

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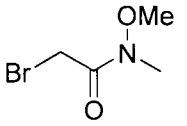
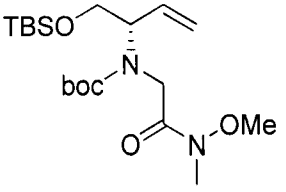


A stirred solution of potassium carbonate (343 g, 2.48 mol) in water (about 800 mL) was prepared and cooled in an ice bath for 15 minutes under nitrogen. To it was added O,N-dimethylhydroxylamine hydrochloride (110 g, 1.13 mol) and diethyl ether (about 800 mL). To this mixture was then added bromoacetyl bromide (273 g, 1.35 mol) by addition funnel over twenty minutes. The ice bath was removed and the mixture was stirred under nitrogen for two hours. The layers were separated and the aqueous layer was extracted with ether (about 350 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The desired product was obtained as a yellow liquid (143 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.24 (s, 3H); 3.80 (s, 3H); 4.01 (s, 2H).

Intermediate 5: (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(2-(methoxy(methyl)amino)-2-oxoethyl)carbamate



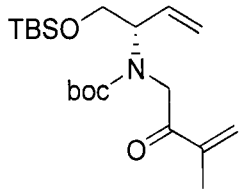
A suspension of (S)-1-(tert-butyldimethylsilyloxy)but-3-en-2-amine (**Intermediate 3**, 60.4 g, 300 mmol) and cesium carbonate (103 g, 315 mmol) in acetonitrile (about 700 mL) and water (about 120 mL) was prepared and stirred in an ice bath under nitrogen for 5 minutes. The mixture was biphasic and remained so for the duration of the reaction. To this mixture was then added 2-bromo-N-methoxy-N-methylacetamide (**Intermediate 4**, 57.0 g, 285 mmol) by addition funnel over 10 minutes. The mixture was stirred for two days, with the temperature maintained near 0 °C. The mixture was kept in the freezer overnight. Analysis by TLC (ethyl acetate, potassium permanganate stain, starting amine R_f ~0.25) indicated high but incomplete conversion of starting amine. Another 0.05 eq of the electrophile was added. The starting amine never disappeared

completely by TLC.

To the mixture was added di-tert-butyl dicarbonate (165 mL, 2M solution in THF); the mixture was stirred until analysis by TLC (ethyl acetate, potassium permanganate stain) indicated consumption of intermediate. The organic layer was separated from the aqueous (TLC indicated that no product remained in the aqueous), and the organic layer was concentrated in vacuo. Silica gel chromatography (5-55% ethyl acetate in hexanes), split into 3 batches, afforded the desired product as a pale yellow oil (80 g, 66%).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.02 (d, J=5.10 Hz, 6 H) 0.84 (s, 9 H) 1.33 (s, 6 H) 1.38 (s, 3 H) 3.02 - 3.15 (m, 3 H) 3.61 - 3.68 (m, 3 H) 3.70 - 3.86 (m, 2 H) 3.95 - 4.12 (m, 2 H) 4.23 - 4.68 (m, 1 H) 5.08 - 5.31 (m, 2 H) 5.75 - 5.96 (m, 1 H).

Intermediate 6: (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(3-methyl-2-oxobut-3-enyl)carbamate



To a solution of (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (**Intermediate 5**, 30.79 g, 76.48 mmol) in THF (200 mL) at 0 °C was added prop-1-en-2-ylmagnesium bromide (0.5M in THF) (300 mL, 149.90 mmol). The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 200 mL 10% citric acid, diluted further with 100 mL water and extracted with ether. The organics were concentrated and the resulting oil was dissolved in ether and washed with water and brine. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-20% ethyl acetate/hexanes) afforded the desired product (26.2 g, 89 %) as a colorless oil.

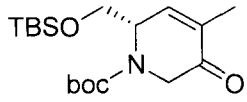
MS: 384 ES+ ($C_{20}H_{37}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.02 (d, 6H); 0.83 (s, 9H); 1.27-1.38 (m, 9H); 1.80 (m, 3H); 3.71 (m, 2H); 4.34 (m, 2H); 4.61 (m, 1H); 5.17 (m, 2H); 5.77 (m, 1H); 5.85 (m, 1H); 6.03 (m,

10/03/2014 08:48 0206

1H).

Intermediate 7: (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate

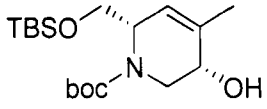


A solution of (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(3-methyl-2-oxobut-3-enyl)carbamate (**Intermediate 6**, 26.18 g, 68.25 mmol) in toluene (600 mL) was purged with nitrogen for 15 minutes. (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (0.987 g, 1.57 mmol) was then added. The reaction mixture was heated at 65 °C for 1.5 hours. The reaction mixture was concentrated onto silica gel. Silica gel chromatography (0%-15% ethyl acetate/hexanes) afforded the desired product (21.18 g, 87 %) as a colorless oil.

MS: 356 ES+ ($C_{18}H_{33}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.01 (d, 6H); 0.81 (s, 9H); 1.42 (s, 9H); 1.75 (m, 3H); 3.74-3.89 (m, 3H); 4.04-4.32 (m, 1H); 4.67 (m, 1H); 6.88 (m, 1H).

Intermediate 8: (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate



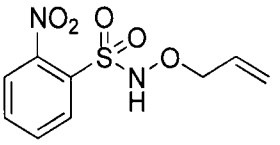
To a solution of cerium(III) chloride (14.68 g, 59.57 mmol) and (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 7**, 21.18 g, 59.57 mmol) in methanol (300 mL) at 0 °C was added sodium borohydride (2.254 g, 59.57 mmol) portionwise. After 15 minutes, the reaction mixture was diluted with saturated ammonium chloride (100 mL) and water (100 mL), then extracted twice with diethyl ether. The organic extracts were washed with brine, dried over magnesium sulfate,

filtered and concentrated. Silica gel chromatography (0%-20% ethyl acetate/hexanes) afforded the desired product (19.45 g, 91 %) as a colorless oil.

MS: 358 ES+ ($C_{18}H_{35}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.02 (s, 6H); 0.86 (s, 9H); 1.39 (s, 9H); 1.69 (m, 3H); 2.63-2.72 (m, 1H); 3.59 (m, 2H); 3.82 (m, 1H); 4.03 (m, 1H); 4.21 (m, 1H); 5.04 (d, 1H); 5.38 (m, 1H).

Intermediate 9: *N*-(allyloxy)-2-nitrobenzenesulfonamide



To a stirred solution of O-allylhydroxylamine hydrochloride (147.05 g, 1341.59 mmol) in DCM (2.5 L) at 0 °C, pyridine (318 mL, 3948 mmol) was added followed by the addition of 2-nitrobenzene-1-sulfonyl chloride (250 g, 1128.05 mmol) portionwise as a solid. The reaction mixture was then stirred at the same temperature for 1 h. Completion of the reaction was monitored by TLC. The reaction mixture was quenched with 1.5 N HCl (1 L). The organic layer was separated, washed with water (250 mL), brine (250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield the residue. The crude was purified by crystallization using EtOAc:petroleum ether (1:3) (800 mL) and afforded 202 g of the title compound as a light brown solid. The mother liquor was concentrated and purified by silica gel column chromatography (mesh 60-120) using petroleum ether:EtOAc (7:3) to yield another 19.1 g of the title compound as a yellow solid. The total yield is 76 %.

UPLC: 257 (M-1) for $C_9H_{10}N_2O_5S$

^{1}HNMR (400 MHz, DMSO-d_6): δ 4.36-4.38 (m, 2H), 5.22-5.32 (m, 2H), 5.84-5.91 (m, 1H), 7.92-7.96 (m, 2H), 8.02-8.05 (m, 2H), 11.07 (s, 1H).

Intermediate 10: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate

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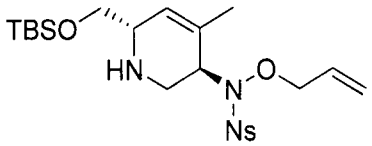
To a solution of (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 8**, 19.45 g, 54.40 mmol) in toluene (300 mL) at room temperature was added triphenylphosphine (17.06 g, 65.28 mmol), N-(allyloxy)-2-nitrobenzenesulfonamide (**Intermediate 9**, 14.05 g, 54.40 mmol) and diisopropyl azodicarboxylate (12.85 mL, 65.28 mmol). After 2 hours the reaction mixture was concentrated onto silica gel and purified. Silica gel chromatography (0%-50% ethyl acetate/hexanes) afforded the desired product (25.2 g, 78 %) as a yellow oil.

MS: 598 ES+ ($C_{27}H_{43}N_3O_8SSi$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.00 (s, 6H); 0.83 (s, 9H); 1.31 (m, 9H); 1.34 (m, 3H); 3.10-3.25 (m, 1H); 3.59 (m, 2H); 3.99-4.41 (m, 5H); 5.17 (m, 2H); 5.72 (m, 2H); 7.93-8.16 (m, 4H).

Intermediate 11: N-(allyloxy)-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1,2,3,6-tetrahydropyridin-3-yl)-2-nitrobenzenesulfonamide



To a solution of (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 10**, 13.38 g, 22.38 mmol) in DCM (200 mL) at room temperature was added zinc bromide (3.36 mL, 67.15 mmol). The reaction mixture was stirred at room temperature overnight then diluted with DCM and washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to afford the desired product as an orange oil (11.14 g, 100%).

MS: 498 ES+ ($C_{22}H_{35}N_3O_6SSi$)

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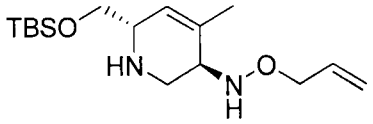
^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.01 (s, 6H); 0.85 (s, 9H); 1.61 (m, 3H); 2.67 (m, 1H); 2.81 (m, 1H); 3.20 (m, 1H); 3.44 (m, 2H); 4.05 (m, 1H); 4.30 (m, 1H); 4.40 (m, 1H); 5.22 (m, 2H); 5.82 (m, 2H); 7.90-8.15 (m, 4H).

Intermediate 12: O-allyl-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1,2,3,6-tetrahydropyridin-3-yl)hydroxylamine

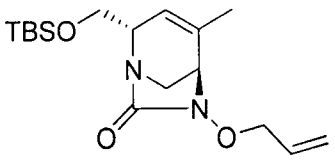


To a solution of N-(allyloxy)-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1,2,3,6-tetrahydropyridin-3-yl)-2-nitrobenzenesulfonamide (**Intermediate 11**, 11.58 g, 23.27 mmol) and potassium carbonate (16.08 g, 116.34 mmol) in acetonitrile (200 mL) at room temperature was added benzenethiol (11.95 mL, 116.34 mmol). After 3 hours, the reaction mixture was concentrated to dryness and DCM was added. The resulting solids were removed by filtration. The filtrate was concentrated onto silica gel. Silica gel chromatography (0%-100% ethyl acetate/hexanes) afforded the desired product (5.06 g, 69.6 %) as an orange oil.

MS: 313 ES+ ($C_{16}H_{32}N_2O_2Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.03 (s, 6H); 0.86 (s, 9H); 1.71 (m, 3H); 2.17 (m, 1H); 2.81 (m, 2H); 3.11 (m, 2H); 3.43 (m, 2H); 4.09 (m, 2H); 5.10-5.25 (m, 2H); 5.48 (m, 1H); 5.87-5.96 (m, 1H); 6.35 (d, 1H).

Intermediate 13: (2S,5R)-6-(allyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1,6-diazabicyclo[3.2.1]oct-3-en-7-one



To a solution of O-allyl-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1,2,3,6-tetrahydropyridin-3-yl)hydroxylamine (**Intermediate 12**, 2 g, 6.40 mmol) and N,N-diisopropylethylamine (4.46 mL, 25.60 mmol) in acetonitrile (555 mL) at 0 °C was added

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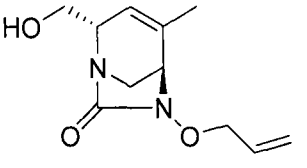
triphosgene (0.760 g, 2.56 mmol) as a solution in acetonitrile (45 mL). The triphosgene solution was added via syringe pump at a rate of 0.1 mL/min. Once addition was complete the reaction was stirred at room temperature overnight. The reaction mixture was concentrated to dryness, diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The aqueous washes were found to contain some product and were extracted twice with ethyl acetate. The combined organics were dried over magnesium sulfate, filtered and combined with previous extracts. Silica gel chromatography (0%-20% ethyl acetate/hexanes) afforded the desired product (1.980 g, 91 %) as a light orange oil.

MS: 339 ES+ ($C_{17}H_{30}N_2O_3Si$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.07 (s, 6H); 0.89 (s, 9H); 1.87 (m, 3H); 3.24 (m, 1H); 3.41 (m, 1H); 3.61 (m, 1H); 3.86 (m, 3H); 4.43 (m, 2H); 5.33 (m, 3H); 6.01 (m, 1H).

Intermediate 14: (2S,5R)-6-(allyloxy)-2-(hydroxymethyl)-4-methyl-1,6-diazabicyclo[3.2.1]oct-3-en-7-one

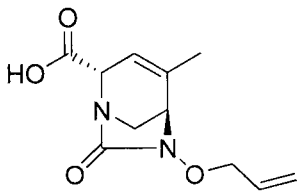


To a solution of (2S,5R)-6-(allyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-1,6-diazabicyclo[3.2.1]oct-3-en-7-one (**Intermediate 13**, 1.76 g, 5.20 mmol) in THF (20 mL) at 0 °C was added tetrabutylammonium fluoride (1M in THF) (6.76 mL, 6.76 mmol). Stirred at 0 °C for 1 hour. The reaction mixture was concentrated onto silca gel. Silica gel chromatography (50%-100% ethyl acetate/hexanes) afforded the desired product (1.070 g, 92 %) as a colorless oil.

MS: 225 ES+ ($C_{11}H_{16}N_2O_3$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.77 (m, 3H); 3.03 (m, 1H); 3.23 (m, 1H); 3.49-3.60 (m, 3H); 3.78 (m, 1H); 4.36 (m, 2H); 4.84 (m, 1H); 5.24-5.39 (m, 3H); 5.90-6.01 (m, 1H).

Intermediate 15: (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid

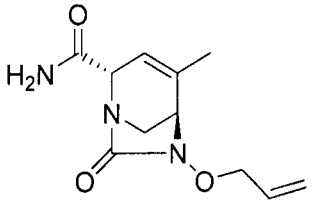


To a solution of periodic acid (2 g, 10.42 mmol) in wet acetonitrile (20 mL) (0.75% water by volume) at room temperature was added chromium(VI) oxide (4 mg, 0.04 mmol). The mixture was stirred until complete dissolution was achieved. This solution (5.47 mL, 3 eq) was added dropwise at 0 °C to a solution of (2S,5R)-6-(allyloxy)-2-(hydroxymethyl)-4-methyl-1,6-diazabicyclo[3.2.1]oct-3-en-7-one (**Intermediate 14**, 0.212 g, 0.95 mmol) in wet acetonitrile (10 mL) (0.75% by volume). The reaction mixture went from clear orange to cloudy brownish color to cloudy green suspension. After 30 minutes, LC/MS showed desired product mass and some remaining starting material. Another equivalent of the oxidizing agent solution (1.82 mL) was added. After 30 minutes, the reaction mixture was diluted with ethyl acetate and washed with 1 to 1 brine/water. The organics were dried over magnesium sulfate, filtered and concentrated to afford a green foam (0.193 g, 86%).

MS: 239 ES+ ($C_{11}H_{14}N_2O_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (m, 3H); 3.19 (m, 2H); 3.85 (m, 1H); 4.27 (m, 1H); 3.37 (m, 2H); 5.28-5.43 (m, 3H); 5.89-6.00 (m, 1H).

Intermediate 16: (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide



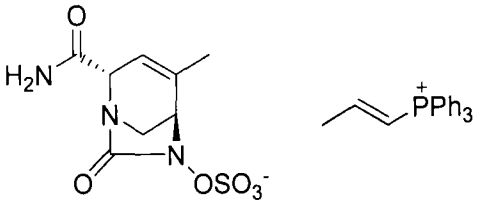
To a solution of (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid (**Intermediate 15**, 0.193 g, 0.81 mmol) in DMF (4 mL) at room temperature was added ammonium chloride (0.130 g, 2.43 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.462 g, 1.22 mmol) and N,N-diisopropylethylamine (0.564 mL, 3.24 mmol). After 10 minutes the reaction mixture was diluted with ethyl acetate and

washed with saturated sodium bicarbonate and brine. The combined aqueous washes were extracted once with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-100% ethyl acetate/hexanes) afforded a brown oil. The oil was taken up in ethyl acetate and washed twice with a 1 to 1 brine/water mixture to remove DMF. The organic layer was dried over magnesium sulfate, filtered and concentrated to afford a light tan foam (0.048 g, 25%).

MS: 238 ES+ ($C_{11}H_{15}N_3O_3$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.79 (m, 3H); 3.19 (m, 2H); 3.81 (m, 1H); 4.12 (m, 1H); 4.36 (m, 2H); 5.24-5.45 (m, 3H); 5.89-6.00 (m, 1H); 7.28 (bs, 1H); 7.49 (bs, 1H).

Intermediate 17: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



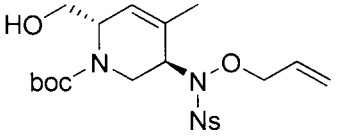
To a solution of (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (**Intermediate 16**, 196.9 mg, 0.83 mmol) and acetic acid (0.095 mL, 1.66 mmol) (dried over sodium sulfate) in DCM (9 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (959 mg, 0.83 mmol). The solution was stirred at room temperature for ~45 minutes and turned dark orange. To the reaction mixture was added pyridine (9.00 mL) and sulfur trioxide-pyridine complex (793 mg, 4.98 mmol). The suspension was stirred overnight at room temperature. The suspension was evaporated to dryness and then resuspended in DCM. The solids were filtered off through a 0.45 μ nalgene filter. The filtrate was concentrated to afford an orange oil. Silica gel chromatography (0%-100% acetone/DCM) afforded the desired product (300 mg, 62.3 %) as a yellow foam.

MS: 278 ES+, 303 ES+ ($C_8H_{10}N_3O_6S$, $C_{21}H_{20}P$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.78 (m, 3H); 2.17 (m, 3H); 3.20 (m, 2H); 3.96 (m, 1H); 4.11 (m, 1H); 5.42 (m, 1H); 6.57-6.74 (m, 1H); 7.22-7.30 (m, 2H); 7.50 (m, 1H); 7.68-7.92 (m, 15H).

Route 2

Intermediate 18: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-(hydroxymethyl)-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate

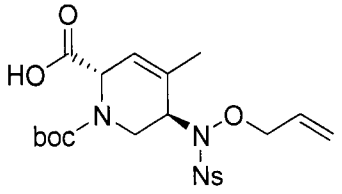


To a solution of (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 10**, 1 g, 1.67 mmol) in THF (11 mL) at 0 °C was added tetrabutylammonium fluoride (1M in THF) (2.175 mL, 2.17 mmol). After 90 minutes the reaction mixture was concentrated onto silica gel. Silica gel chromatography (0%-70% ethyl acetate/hexanes) afforded the desired product (0.732 g, 90 %) as a tan foam.

MS: 484 ES+ ($C_{21}H_{29}N_3O_8S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.31 (m, 9H); 1.35 (m, 3H); 3.20 (m, 1H); 3.41 (m, 2H); 3.96-4.37 (m, 5H); 4.76 (m, 1H); 5.19 (m, 2H); 5.66-5.84 (m, 2H); 7.94-8.18 (m, 4H).

Intermediate 19: (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-1-(tert-butoxycarbonyl)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid



To a solution of periodic acid (6 g, 31.26 mmol) in wet acetonitrile (60 mL) (0.75% water by volume) at room temperature was added chromium(VI) oxide (10 mg, 0.10 mmol). The mixture was stirred until complete dissolution was achieved.

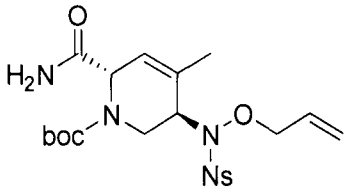
To a solution of (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-(hydroxymethyl)-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 18**, 5 g, 10.34 mmol) in wet acetonitrile (60 mL) (0.75% by volume) at 0 °C was added dropwise the previously formed periodic acid/chromium oxide solution (60 mL, 3 eq). After 30 minutes the reaction was

complete by LC/MS. The reaction mixture was diluted with ether and washed with 10% citric acid, saturated sodium bicarbonate and brine. The organics were dried over magnesium sulfate, filtered and concentrated to afford an orange foam (4.16 g, 81%).

MS: 498 ES+ ($C_{21}H_{27}N_3O_9S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.26 (m, 9H); 1.31 (m, 3H); 3.02-3.25 (m, 1H); 3.90 (m, 1H); 4.17 (m, 3H); 4.65-4.77 (m, 1H); 5.12-5.21 (m, 2H); 5.68 (m, 1H); 5.88 (m, 1H); 7.92-8.17 (m, 4H).

Intermediate 20: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-carbamoyl-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate



To a solution of (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-1-(tert-butoxycarbonyl)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid (**Intermediate 19**, 4.16 g, 8.36 mmol) in DMF (35 mL) at room temperature was added ammonium chloride (0.895 g, 16.72 mmol), HATU (4.77 g, 12.54 mmol) and DIEA (5.84 mL, 33.45 mmol). After 15 minutes the reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and twice with 1:1 brine:water. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-80% ethyl acetate/hexanes) was run twice to afforded the desired product (2.16 g, 52 %) as a yellow foam.

MS: 497 ES+ ($C_{21}H_{28}N_4O_8S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.26 (m, 9H); 1.37 (m, 3H); 3.12-3.35 (m, 1H); 3.80 (m, 1H); 4.18 (m, 3H); 4.64-4.79 (m, 1H); 5.13-5.22 (m, 2H); 5.68 (m, 1H); 5.88 (m, 1H); 7.04 (m, 1H); 7.45 (bs, 1H); 7.90-8.18 (m, 4H).

Intermediate 21: (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide

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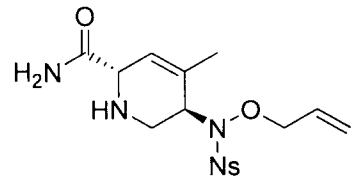
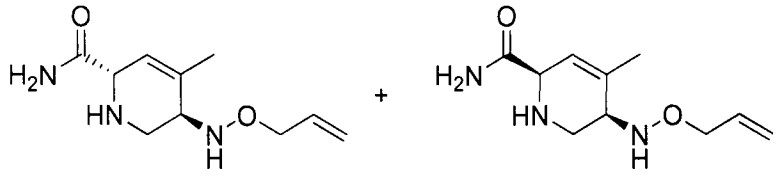


To a solution of (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-carbamoyl-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 20**, 2.16 g, 4.35 mmol) in DCM (20 mL) at room temperature was added zinc bromide (0.700 mL, 13.05 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate and brine. The organics were dried over magnesium sulfate, filtered and concentrated to afford the desired product (1.450 g, 84 %) as a yellow foam.

MS: 397 ES+ ($C_{16}H_{20}N_4O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.65 (m, 3H); 2.71 (m, 3H); 3.76 (m, 1H); 3.95 (m, 1H); 4.18-4.42 (m, 2H); 5.23 (m, 2H); 5.82 (m, 1H); 6.02 (m, 1H); 7.05 (bs, 1H); 7.30 (bs, 1H); 7.93-8.18 (m, 4H).

Intermediate 22: (2S,5R)-5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide and (2R,5R)-5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide



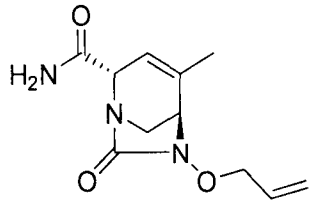
To a solution of (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide (**Intermediate 21**, 1.4 g, 3.53 mmol) and cesium carbonate (9.21 g, 28.25 mmol) in THF (100 mL) at room temperature was added PS-thiophenol (3-(3-mercaptophenyl)propanamidomethylpolystyrene) (1.55 mmol/g) (9.12 g, 14.13 mmol). After stirring overnight at room temperature, the reaction mixture was filtered through a fritted funnel and the resin was washed twice with DCM. The filtrate was concentrated to afford a yellow oil.

Silica gel chromatography (0%-5% methanol/dichloromethane) afforded a 3 to 1 mixture of trans and cis isomers (0.473 g, 63.4 %) as a light yellow oil. The mixture was taken forward without separation.

MS: 212 ES+ ($C_{10}H_{17}N_3O_2$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.73 (m, 3H); 2.63 (m, 1H); 2.97 (m, 1H); 3.01 (m, 1H); 3.60 (m, 1H); 4.12 (m, 2H); 5.11-5.26 (m, 2H); 5.92 (m, 1H); 6.45 (m, 1H); 7.00 (m, 1H); 7.33 (bs, 1H).

Intermediate 16: (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide



To a solution of (2S,5R)-5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide and (2R,5R)-5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide (**Intermediate 22**, 0.429 g, 2.03 mmol) and N,N-diisopropylethylamine (1.415 mL, 8.12 mmol) in acetonitrile (170 mL) at 0 °C was added triphosgene (0.241 g, 0.81 mmol) as a solution in acetonitrile (1.5 mL). The triphosgene solution was added at a rate of 0.1 mL/min. Once addition was complete the reaction was warmed to room temperature and stirred over weekend. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-20% ethyl acetate/hexanes) afforded (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (0.312 g, 64.8 %) as a light yellow oil.

MS: 238 ES+ ($C_{11}H_{15}N_3O_3$)

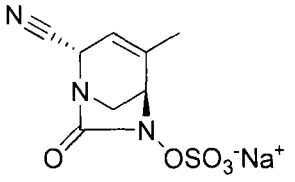
^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.79 (m, 3H); 3.19 (m, 2H); 3.81 (m, 1H); 4.12 (m, 1H); 4.36 (m, 2H); 5.24-5.45 (m, 3H); 5.89-6.00 (m, 1H); 7.28 (bs, 1H); 7.49 (bs, 1H).

The final two steps of Route 2 to yield Example 1 are equivalent for those shown for above for

Route 1.

EXAMPLE 2

(2S,5R)-2-cyano-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt



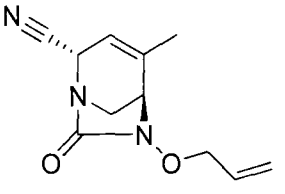
The title compound was prepared from (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-cyano-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 24**, 0.1167 g, 0.21 mmol) following the procedure described for **Example 1** above. The desired product was obtained as a white solid (53.6 mg, 91%).

Optical rotation: (0.1 g/dL, DMSO) = -262

MS: 258 ES- ($C_8H_9N_3O_5S$)

^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.82 (s, 3H); 3.26 (m, 1H); 3.44 (m, 1H); 4.08 (m, 1H); 4.95 (m, 1H); 5.33 (m, 1H).

Intermediate 23: (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carbonitrile



To a solution of (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (**Intermediate 16**, 146 mg, 0.62 mmol) in DCM (6 mL), under nitrogen, at room temperature was added methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide inner salt (Burgess Reagent) (660 mg, 2.77 mmol) portionwise over 2 hours. The reaction was stirred at room temperature for an additional 30 minutes. The reaction mixture was washed with 1:1 brine:water. The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-25% ethyl acetate/hexanes) afforded (2S,5R)-6-(allyloxy)-4-

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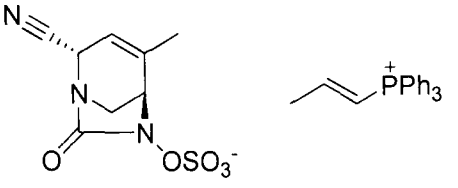
methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carbonitrile (112 mg, 83 %) as a colorless oil.

MS: 220 ES+ ($C_{11}H_{13}N_3O_2$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.83 (m, 3H); 3.27 (m, 1H); 3.40 (m, 1H); 3.97 (m, 1H); 4.38 (m, 2H); 4.97 (m, 1H); 5.26-5.39 (m, 3H); 5.88-5.99 (m, 1H).

Intemediate 24: (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carbonitrile



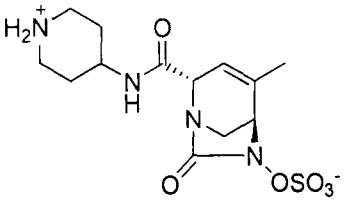
The title compound was prepared from (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carbonitrile (**Intermediate 23**, 111.8 mg, 0.51 mmol) following the procedure described for **Intermediate 17**. The desired product was obtained as an off-white foam (117 mg, 40.8%).

MS: 258 ES-, 303 ES+ ($C_8H_8N_3O_5S$, $C_{21}H_{20}P$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.83 (m, 3H); 2.17 (m, 3H); 3.26 (m, 1H); 3.45 (m, 1H); 4.08 (m, 1H); 4.94 (m, 1H); 5.33 (m, 1H); 6.59-6.72 (m, 1H); 7.22-7.39 (m, 1H); 7.68-7.92 (m, 15H).

EXAMPLE 3

(2S,5R)-4-methyl-7-oxo-2-(piperidinium-4-ylcarbamoyl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



To a solution of (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 26**, 0.1521 g, 0.20 mmol) in DCM (3 mL) at 0 °C was added

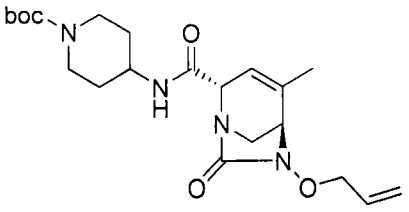
trifluoroacetic acid (0.031 mL, 0.40 mmol). After 30 minutes more trifluoroacetic acid (0.031 mL, 0.40 mmol) was added. After another 30 minutes, another 6 equivalents of TFA was added at 0 °C. Reaction mixture was allowed to warm to room temperature. After 1 hour, the reaction was not complete. The reaction mixture was stored in the freezer overnight. In the morning, another 5 eq TFA were added at 0 °C. Reaction allowed to warm to room temperature. After 4 hours, the reaction mixture was concentrated and coevaported with DCM three times. The sticky oil was then triturated with ether and concentrated to afford a yellow solid. The solid was dissolved in water and washed twice with DCM. The aqueous phase was lyophilized. Purification was done on reverse phase HPLC (0-10% methanol in water, YMC Carotenoid C30, 19mm x 150mm, 5μm) to afford the title compound as a white solid (3 mg, 4.3%).

MS: 361 ES+ ($C_{13}H_{20}N_4O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.53 (m, 3H); 1.73 (m, 3H); 1.78 (m, 3H); 2.82 (m, 3H); 3.16 (m, 2H); 3.77 (m, 1H); 3.97 (m, 1H); 4.14 (m, 1H); 5.37 (m, 1H); 6.49 (m, 1H); 8.13 (m, 1H).

Route 1

Intermediate 25: tert-butyl 4-((2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-enecarboxamido)piperidine-1-carboxylate



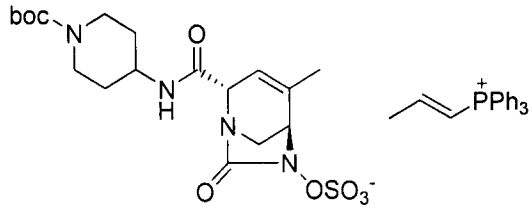
To a solution of (2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid (**Intermediate15**, 0.407 g, 1.71 mmol) in DMF (7 mL) at room temperature was added 1-Boc-4-amino-piperidine hydrochloride (0.809 g, 3.42 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.299 g, 3.42 mmol) and N,N-diisopropylethylamine (1.190 mL, 6.83 mmol). After 30 minutes, the reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, brine and 1/1 brine/water. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-60% ethyl acetate/hexanes) afforded the desired product (0.502 g, 69.9

%) as an off-white foam.

MS: 421 ES+ ($C_{21}H_{32}N_4O_5$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.32 (m, 2H); 1.39 (s, 9H); 1.66 (m, 2H); 1.79 (m, 3H); 2.81 (m, 2H); 3.14 (m, 1H); 3.32 (m, 1H); 3.73 (m, 1H); 3.84 (m, 3H); 4.14 (m, 1H); 4.36 (m, 2H); 5.24-5.42 (m, 3H); 5.88-6.02 (m, 1H); 8.00 (m, 1H).

Intermediate 26: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



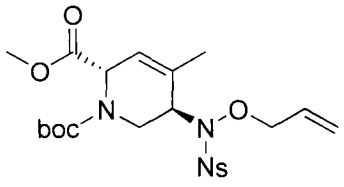
To a solution of tert-butyl 4-((2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-enecarboxamido)piperidine-1-carboxylate (**Intermediate 25,** 0.502 g, 1.19 mmol) and acetic acid (0.137 mL, 2.39 mmol) (dried over sodium sulfate) in DCM (15 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (0.690 g, 0.60 mmol). The solution was stirred at room temperature for 30 minutes and turned from yellow to orange. To the reaction mixture was added pyridine (15 mL) and sulfur trioxide-pyridine complex (1.520 g, 9.55 mmol). The suspension was stirred overnight at room temperature. The suspension was evaporated to dryness and then resuspended in DCM. The solids were filtered off through a 0.45 μ nalgene filter. The filtrate was concentrated to afford an orange oil. Silica gel chromatography (0%-50% acetone/DCM) afforded the desired product (0.152 g, 16.7 %) as a white foam.

MS: 459 ES-, 303 ES+ ($C_{18}H_{27}N_4O_8S$, $C_{21}H_{20}P$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.36 (m, 2H); 1.41 (s, 9H); 1.68 (m, 2H); 1.78 (m, 3H); 2.11 (m, 2H); 2.18 (m, 2H); 2.83 (m, 2H); 3.20 (m, 1H); 3.31 (m, 1H); 3.76 (m, 1H); 3.87 (m, 2H); 3.98 (m, 1H); 4.14 (m, 1H); 5.40 (m, 1H); 6.59-6.74 (m, 1H); 7.24-7.33 (m, 1H); 7.69-8.01 (m, 15H).

Route 2

Intermediate 27: (2S,5R)-1-tert-butyl 2-methyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-methyl-5,6-dihydropyridine-1,2(2H)-dicarboxylate

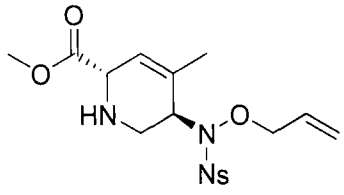


To a solution of (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-1-(tert-butoxycarbonyl)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid (**Intermediate 19**, 3 g, 6.03 mmol) and potassium carbonate (3.33 g, 24.12 mmol) in DMF (30 mL) at room temperature was added methyl iodide (0.454 mL, 7.24 mmol). After 1 hour the reaction mixture was diluted with ethyl acetate and washed three times with water. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-30% ethyl acetate/hexanes) afforded the desired product (2.060 g, 66.8 %) as an off-white foam.

MS: 512 ES+ ($C_{22}H_{29}N_3O_9S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.27 (m, 9H); 1.71 (m, 3H); 2.98-3.19 (m, 1H); 3.65 (m, 3H); 3.91 (m, 1H); 4.17 (m, 3H); 4.81-4.96 (m, 1H); 5.12-5.21 (m, 2H); 5.67 (m, 1H); 5.86 (m, 1H); 7.94-8.17 (m, 4H).

Intermediate 28: (2S,5R)-methyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate



To a solution of (2S,5R)-1-tert-butyl 2-methyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-methyl-5,6-dihydropyridine-1,2(2H)-dicarboxylate (**Intermediate 27**, 2.06 g, 4.03 mmol) in DCM (20 mL) at room temperature was added zinc bromide (0.648 mL, 12.08 mmol). After stirring overnight, the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate and brine. The organics were dried over magnesium sulfate, filtered and concentrated to afford the desired product (1.650 g, 100 %) as a light yellow foam.

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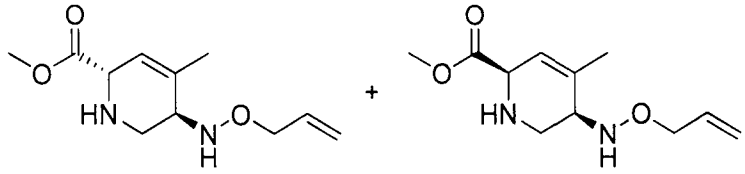
MS: 412 ES+ ($C_{17}H_{21}N_3O_7S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.56 (m, 3H); 2.68 (m, 1H); 2.91 (m, 1H); 3.61 (s, 3H); 4.01 (m, 2H); 4.28 (m, 1H); 4.48 (m, 1H); 5.18-5.28 (m, 2H); 5.85 (m, 2H); 7.91-8.17 (m, 4H).

Intermediate 29: (2S,5R)-methyl 5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate and (2R,5R)-methyl 5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate



To a solution of (2S,5R)-methyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate (**Intermediate 28**, 1.65 g, 4.01 mmol) and cesium carbonate (7.84 g, 24.06 mmol) in THF (100 mL) at room temperature was added PS-thiophenol (3-(3-mercaptophenyl)propanamidomethylpolystyrene) (1.55 mmol/g) (7.76 g, 12.03 mmol). After 3 hours the reaction mixture was filtered and the resin was washed with DCM. The filtrate was concentrated to afford a yellow oil. Silica gel chromatography (0%-50% methanol/DCM) afforded a 1 to 1 mixture of (2S,5R)-methyl 5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate and (2R,5R)-methyl 5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate (0.680 g, 74.9 %) as an orange oil. The mixture was taken forward without separation.

MS: 227 ES+ ($C_{11}H_{18}N_2O_3$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.74 (m, 6H); 2.70 (m, 3H); 3.03 (m, 4H); 3.61 (s, 3H); 3.64 (s, 3H); 3.90 (m, 2H); 4.10 (m, 4H); 5.11-5.25 (m, 5H); 5.60 (m, 2H); 5.91 (m, 2H); 6.25 (m, 1H); 6.41 (m, 1H).

Intermediate 30 and Intemediate 31: (2S,5R)-methyl 6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylate and (2R,5R)-methyl 6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylate

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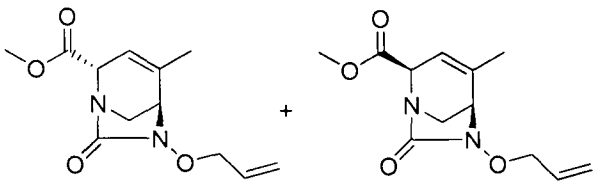


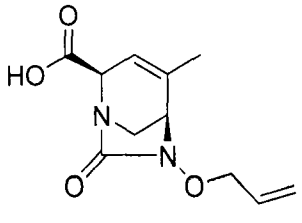
To a solution of (2S,5R)-methyl 5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate and (2R,5R)-methyl 5-(allyloxyamino)-4-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate (1 to 1 mixture) (**Intermediate 29**, 0.68 g, 3.01 mmol) and N,N-diisopropylethylamine (2.094 mL, 12.02 mmol) in acetonitrile (250 mL) at 0 °C was added triphosgene (0.357 g, 1.20 mmol) as a solution in acetonitrile (3 mL). The triphosgene solution was added via syringe pump at a rate of 1 mL/hr. Once addition was complete, the reaction was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-60% ethyl acetate/hexanes) afforded the desired trans product (**Intermediate 30**, 0.292 g, 38%) and the undesired cis product (**Intermediate 31**, 0.191 g, 25%). The cis isomer can be converted to the trans isomer by stirring in acetonitrile with 3 equivalents of triethylamine for 1 hour, followed by similar work as for the reaction mixture.

MS: 253 ES+ ($C_{12}H_{16}N_2O_4$) for both cis and trans

^{1}H NMR (300 MHz, DMSO-d_6) trans **Intermediate 30** δ: 1.80 (m, 3H); 3.12 (m, 1H); 3.22 (m, 1H); 3.69 (s, 3H); 3.87 (m, 1H); 4.38 (m, 3H); 5.24-5.42 (m, 3H); 5.94 (m, 1H).

^{1}H NMR (300 MHz, DMSO-d_6) cis **Intermediate 31** δ: 1.82 (m, 3H); 3.19 (m, 1H); 3.34 (m, 1H); 3.64 (s, 3H); 3.89 (m, 1H); 4.34 (m, 2H); 4.61 (m, 1H), 5.23-5.37 (m, 2H); 5.50 (m, 1H); 5.92 (m, 1H).

Intermediate 32: (2R,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid

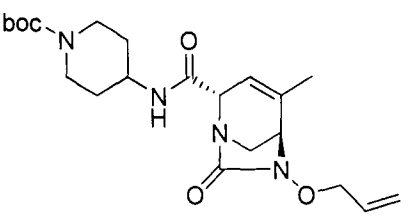


To a solution of (2S,5R)-methyl 6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylate (**Intermediate 30**, 0.479 g, 1.90 mmol) in THF (10 mL) and water (5 mL) at 0 °C was added lithium hydroxide (0.045 g, 1.90 mmol). The reaction was stirred at 0 °C for 2 hours. Another 0.5 eq lithium hydroxide was added. After 2 hours the reaction mixture was neutralized carefully with 1N HCl at 0 °C and the THF was evaporated. The aqueous was frozen and lyophilized to afford a light orange solid (0.464 g, 103% crude).

MS: 239 ES+ ($C_{11}H_{14}N_2O_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.72 (m, 3H); 2.38 (m, 1H); 3.00 (m, 1H); 3.47 (m, 1H); 3.68 (m, 1H); 3.83 (m, 1H); 4.33 (m, 1H); 5.15-55 (m, 4H); 5.94 (m, 1H).

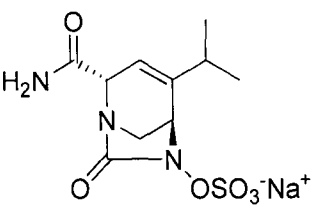
Intermediate 25: tert-butyl 4-((2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-enecarboxamido)piperidine-1-carboxylate



The title compound was prepared from (2R,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid (**Intermediate 32**) following the procedure described in Route 1 for **Intermediate 25**. See Route 1 for final 2 steps.

EXAMPLE 4

(2S,5R)-2-carbamoyl-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt



The title compound was prepared from (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 44**,

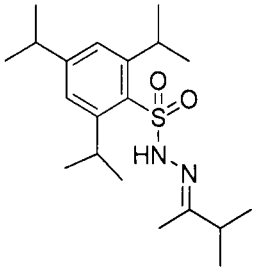
71.1 mg, 0.12 mmol) following the procedure described for **Example 1**. The desired product was obtained as a light yellow solid (31.9 mg, 83%).

Optical rotation: (0.1 g/dL, MeOH) = -212

MS: 306 ES+ ($C_{10}H_{15}N_3O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.99 (m, 6H); 2.27 (m, 1H); 3.15 (m, 1H); 3.26 (m, 1H); 4.12 (m, 2H); 5.38 (m, 1H); 7.26 (bs, 1H); 7.52 (bs, 1H).

Intermediate 33: (E)-2,4,6-triisopropyl-N'-(3-methylbutan-2-ylidene)benzene-sulfonohydrazide

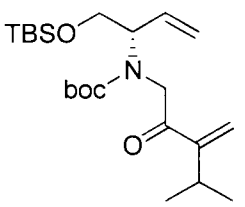


To a suspension of 2,4,6-triisopropylbenzenesulfonyl hydrazide (5.06 g, 16.95 mmol) and 3-methylbutan-2-one (1.814 mL, 16.95 mmol) in ethanol (20 mL) was added 2 drops of concentrated hydrochloric acid. The suspension became a solution and within a minute or two a white solid began to precipitate. The reaction mixture was placed in the fridge for 2 hours. The white precipitate was collected by filtration to afford the desired product (4.44 g, 71%).

MS: 367 ES+ ($C_{20}H_{34}N_2O_2S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.87 (d, 6H); 1.17 (m, 18H); 1.75 (s, 3H); 2.31 (m, 1H); 2.90 (m, 1H); 4.24 (m, 2H); 7.19 (s, 2H); 9.96 (s, 1H).

Intermediate 34: (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(4-methyl-3-methylene-2-oxopentyl)carbamate

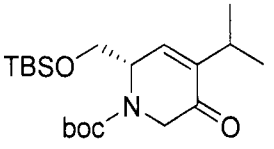


To a suspension of (E)-2,4,6-triisopropyl-N'-(3-methylbutan-2-ylidene)benzenesulfonohydrazide (**Intermediate 33**, 8 g, 21.82 mmol) in hexane (65 mL) and TMEDA (6.50 mL) at -78 °C was added dropwise n-butyllithium (1.6M in hexanes) (34.1 mL, 54.56 mmol). The reaction mixture turned orange and was stirred for 30 minutes at -78 °C, then was warmed to 0 °C and bubbling started immediately. The suspension became a yellow solution. After ~15 minutes the bubbling stopped and (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(2-(methoxy(methyl)-amino)-2-oxoethyl)carbamate (**Intermediate 5**, 4.39 g, 10.91 mmol) was added as a solution in hexane (2 mL). After ~15 minutes LC/MS shows desired product and no remaining Weinreb amide starting material. The reaction mixture was quenched with saturated sodium bicarbonate and extracted with ether twice. The ether extracts were dried over magnesium sulfate, filtered and concentrated to afford a yellow oil. Silica gel chromatography (0%-10% ethyl acetate/hexanes) afforded the desired product (2.219 g, 49.4 %) as a light yellow oil.

MS: 412 ES+ ($C_{22}H_{41}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.01 (m, 6H); 0.82 (m, 9H); 0.98 (m, 6H); 1.28-1.38 (m, 9H); 2.77 (m, 1H); 3.71 (m, 2H); 4.33 (m, 2H); 4.62 (m, 1H); 5.16 (m, 2H); 5.77 (m, 2H); 6.06 (m, 1H).

Interemediate 35: (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-isopropyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate



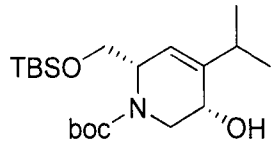
The title compound was prepared from (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(4-methyl-3-methylene-2-oxopentyl)carbamate (**Intermediate 34**, 0.839 g, 2.04 mmol)

following the procedure described for **Intermediate 7**, using 0.32 eq of (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium. The desired product was obtained as a colorless oil (0.667 g, 85%).

MS: 384 ES+ ($C_{20}H_{37}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.00 (m, 6H); 0.80 (s, 9H); 1.00 (m, 6H); 1.42 (s, 9H); 2.77 (m, 1H); 3.85 (m, 3H); 4.26 (m, 1H); 4.69 (m, 1H); 6.80 (m, 1H).

Intermediate 36: (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate

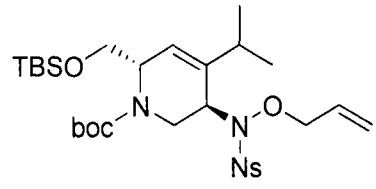


The title compound was prepared from (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-isopropyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 35**, 0.667 g, 1.74 mmol) following the procedure described for **Intermediate 8**. The desired product was obtained as a colorless oil (0.464 g, 69%).

MS: 386 ES+ ($C_{20}H_{39}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.02 (s, 6H); 0.86 (s, 9H); 0.98 (s, 6H); 1.39 (s, 9H); 2.64 (m, 2H); 3.59 (m, 2H); 3.99 (m, 2H); 4.21 (m, 1H); 5.04 (d, 1H); 5.36 (m, 1H).

Intermediate 37: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate



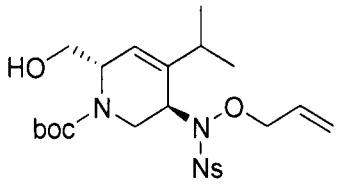
The title compound was prepared from (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 36**, 1.2 g, 3.11

mmol) following the procedure described for **Intermediate 10**, using 2.4 equivalents each of triphenylphosphine and diisopropylazodicarboxylate. The desired product was obtained as yellow foam (1.22 g, 62%).

MS: 626 ES+ ($C_{29}H_{47}N_3O_8SSi$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.00 (s, 6H); 0.83 (s, 9H); 1.00 (m, 6H); 1.34 (m, 9H); 3.18 (m, 1H); 3.59 (m, 2H); 4.22 (m, 4H); 4.46 (m, 1H); 5.18 (m, 2H); 5.73 (m, 2H); 7.91-8.18 (m, 4H).

Intermediate 38: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-(hydroxymethyl)-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate

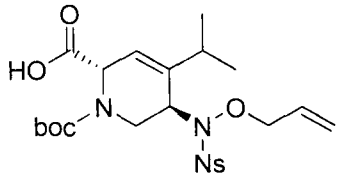


The title compound was prepared from (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 37**, 0.361 g, 0.58 mmol) following the procedure described for **Intermediate 18**. The desired product was obtained as a tan foam (0.257 g, 87%).

MS: 512 ES+ ($C_{23}H_{33}N_3O_8S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.93 (m, 6H); 1.35 (m, 9H); 3.13 (m, 1H); 3.40 (m, 2H); 4.18 (m, 3H); 4.41 (m, 1H); 4.75 (m, 1H); 5.20 (m, 2H); 5.74 (m, 2H); 7.92-8.19 (m, 4H).

Intermediate 39: (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-1-(tert-butoxycarbonyl)-4-isopropyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid

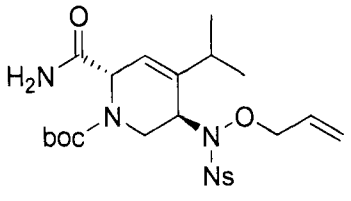


The title compound was prepared from (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-(hydroxymethyl)-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 38**, 0.727 g, 1.42 mmol) following the procedure described for **Intermediate 19**. The desired product was obtained as an off-white foam (0.65 g, 87%).

MS: 526 ES+ ($C_{23}H_{31}N_3O_9S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.00 (m, 6H); 1.26 (m, 9H); 2.95-3.13 (m, 1H); 3.95 (m, 1H); 4.10-4.34 (m, 3H); 4.77-4.91 (m, 1H); 5.19 (m, 2H); 5.67-5.87 (m, 2H); 7.92-8.20 (m, 4H).

Intermediate 40: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-carbamoyl-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate



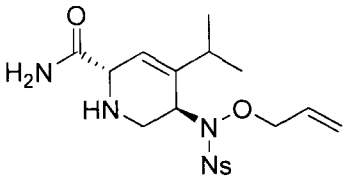
The title compound was prepared from (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-1-(tert-butoxycarbonyl)-4-isopropyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid (**Intermediate 39**, 0.65 g, 1.24 mmol) following the procedure described for **Intermediate 20**. The desired product was obtained as an off-white solid (0.322 g, 51%).

MS: 525 ES+ ($C_{23}H_{32}N_4O_8S$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (m, 6H); 1.31 (m, 9H); 3.20 (m, 1H); 4.20 (m, 3H); 4.70-4.87 (m, 1H); 5.19 (m, 2H); 5.69 (m, 1H); 5.86 (m, 1H); 7.03 (m, 1H); 7.47 (m, 1H); 7.94-8.21 (m, 4H).

Intermediate 41: (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-isopropyl-1,2,5,6-

tetrahydropyridine-2-carboxamide

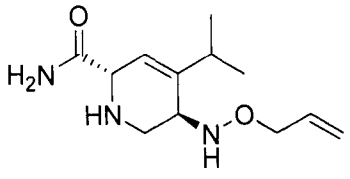


The title compound was prepared from (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-carbamoyl-4-isopropyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 40**, 0.427 g, 0.81 mmol) following the procedure described for **Intermediate 21**. The desired product was obtained as yellow foam (0.247 g, 71%).

MS: 425 ES+ ($C_{18}H_{24}N_4O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.95 (m, 6H); 2.25 (m, 1H); 2.67 (m, 2H); 3.81 (m, 1H); 4.07 (m, 1H); 4.30 (m, 2H); 5.24 (m, 2H); 5.83 (m, 1H); 6.03 (m, 1H); 7.03 (m, 1H); 7.32 (m, 1H); 7.93-8.18 (m, 4H).

Intermediate 42: (2S,5R)-5-(allyloxyamino)-4-isopropyl-1,2,5,6-tetrahydropyridine-2-carboxamide

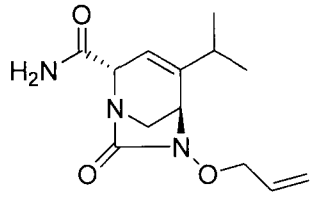


The title compound was prepared from (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-4-isopropyl-1,2,5,6-tetrahydropyridine-2-carboxamide (**Intermediate 41**, 0.247 g, 0.58 mmol) following the procedure described for **Intermediate 22**. The desired product was obtained as a light yellow solid (98 mg, 71%)

MS: 240 ES+ ($C_{12}H_{21}N_3O_2$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.99 (m, 6H); 2.37 (m, 1H); 3.04 (m, 1H); 3.17 (m, 1H); 3.60 (m, 1H); 4.11 (m, 2H); 5.11-5.26 (m, 2H); 5.78 (m, 1H); 5.86-6.00 (m, 1H); 6.31 (m, 1H); 7.01 (bs, 1H); 7.36 (bs, 1H).

Intermediate 43: (2S,5R)-6-(allyloxy)-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide

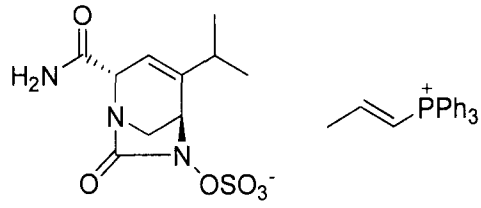


The title compound was prepared from (2S,5R)-5-(allyloxyamino)-4-isopropyl-1,2,5,6-tetrahydropyridine-2-carboxamide (0.0981 g, 0.41 mmol) and N,N-diisopropylethylamine (**Intermediate 42**, 0.286 mL, 1.64 mmol) following the procedure described for **Intermediate 16**. The desired product was obtained as a light yellow oil (69 mg, 63%).

MS: 266 ES+ ($C_{13}H_{19}N_3O_3$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.00 (m, 6H); 2.28 (m, 1H); 3.19 (m, 2H); 4.02 (m, 1H); 4.14 (m, 1H); 4.37 (m, 2H); 5.28-5.42 (m, 3H); 5.90-6.01 (m, 1H); 7.28 (bs, 1H); 7.51 (bs, 1H).

Intermediate 44: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



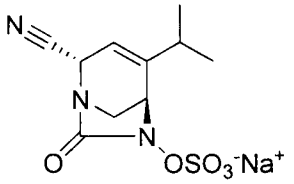
The title compound was prepared from 2S,5R)-6-(allyloxy)-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (**Intermediate 43**, 68.7 mg, 0.26 mmol) following the procedure described for **Intermediate 17**, using 1 equivalent of tetrakis(triphenylphosphine)-palladium. The desired product was obtained as a yellow oil (71 mg, 45%).

MS: 306 ES+, 303 ES+ ($C_{10}H_{15}N_3O_6S$, $C_{21}H_{20}P$)

EXAMPLE 5

(2S,5R)-2-cyano-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate

sodium salt



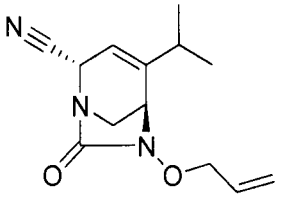
The title compound was prepared from (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-cyano-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 46**, 47.2 mg, 0.08 mmol) following the procedure described for **Example 1**. The desired product was obtained as a white solid (18.2 mg, 73%).

Optical rotation: (0.1 g/dL, DMSO) = -168

MS: 286 ES- ($C_{10}H_{13}N_3O_5S$)

^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.00 (m, 6H); 2.30 (m, 1H); 3.20 (m, 1H); 3.50 (m, 1H); 4.24 (m, 1H); 4.97 (m, 1H); 5.25 (m, 1H).

Intermediate 45: (2S,5R)-6-(allyloxy)-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carbonitrile



The title compound was prepared from 2S,5R)-6-(allyloxy)-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (**Intermediate 43**, 143.9 mg, 0.54 mmol) following the procedure described for **Intermediate 23**. The desired product was obtained as a colorless oil (114 mg, 85%).

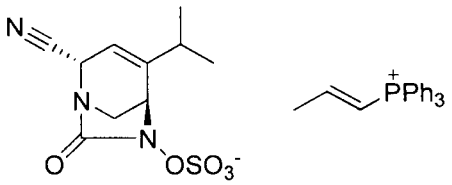
MS: 248 ES+ ($C_{13}H_{17}N_3O_2$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.00 (m, 6H); 2.32 (m, 1H); 3.21 (m, 1H); 3.45 (m, 1H); 4.18 (m, 1H); 4.38 (m, 2H); 4.98 (m, 1H); 5.25-5.39 (m, 3H); 5.86-6.00 (m, 1H).

Intermediate 46: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-cyano-4-isopropyl-7-

10/03/2014 08:45:03 4

oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



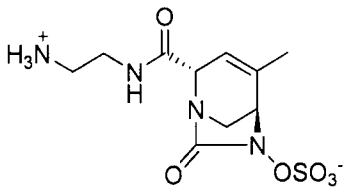
The title compound was prepared from (2S,5R)-6-(allyloxy)-4-isopropyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carbonitrile (**Intermediate 45**, 114.1 mg, 0.46 mmol) following the procedure described for **Intermediate 17**, using 0.75 equivalents of tetrakis(triphenyl-phosphine)palladium. The desired product was obtained as a light yellow oil (47.2 mg, 17%).

MS: 286 ES-, 303 ES+ ($C_{10}H_{12}N_3O_5S$, $C_{21}H_{20}P$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.01 (m, 6H); 2.17 (m, 3H); 3.21 (m, 1H); 3.50 (m, 1H); 4.24 (m, 1H); 4.98 (m, 1H); 5.26 (m, 1H); 6.64-6.73 (m, 1H); 7.23-7.37 (m, 1H); 7.51-7.65 (m, 1H); 7.68-7.95 (m, 15H).

EXAMPLE 6

(2S,5R)-2-(2-aminoethylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate



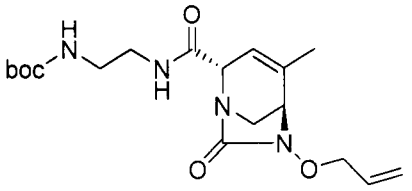
To a solution of (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-(2-(tert-butoxycarbonylamino)ethylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 48**, 0.238 g, 0.33 mmol) in DCM (2 mL) at 0 °C was added TFA (2 mL). After 30 minutes the reaction mixture was concentrated to afford an orange oil. The oil was triturated with ether three times and ethyl acetate three times to afford an orange solid. Purification was done on reverse phase HPLC (0-10% acetonitrile in water, YMC Carotenoid C30, 19mm x 150mm, 5μm) to afford the title compound as a white solid (25.4 mg, 13%).

Optical rotation: (0.1 g/dL, DMSO) = -120.

MS: 321 ES+ ($C_{10}H_{16}N_4O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (m, 3H); 2.88 (m, 2H); 3.17 (m, 1H); 3.24 (m, 1H); 3.39 (m, 2H); 3.99 (m, 1H); 4.21 (m, 1H); 4.48 (m, 1H); 7.43 (m, 2H); 8.25 (m, 1H).

Intermediate 47: tert-butyl 2-((2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-enecarboxamido)ethylcarbamate

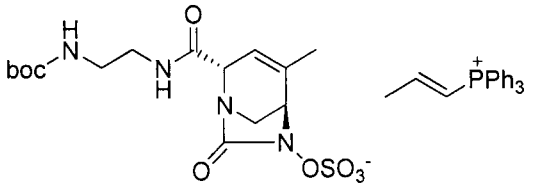


The title compound was prepared from (2R,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid (**Intermediate 15**, 0.348 g, 1.46 mmol) and N-Boc-ethylenediamine hydrochloride (0.287 g, 1.46 mmol) following the precedure described for **Intermediate 25**. The desired product was obtained as a light pink foam (230 mg, 41%).

MS: 381 ES+ ($C_{18}H_{28}N_4O_5$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.37 (s, 9H); 1.79 (m, 3H); 3.00 (m, 2H); 3.16 (m, 4H); 3.82 (m, 1H); 4.14 (m, 1H); 4.37 (m, 2H); 5.24-5.47 (m, 3H); 5.90-6.00 (m, 1H); 6.81 (m, 1H); 8.07 (m, 1H).

Intermediate 48: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-(2-(tert-butoxy-carbonylamino)ethylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



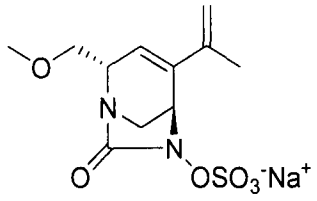
To a solution of tert-butyl 2-((2S,5R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-enecarboxamido)ethylcarbamate (**Intermediate 47**, 230 mg, 0.60 mmol) and acetic acid (0.069 mL, 1.21 mmol) (dried over sodium sulfate) in DCM (9 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (349 mg, 0.30 mmol). The solution was stirred at room

temperature for 1 hour. To the reaction mixture was added pyridine (9.00 mL) and sulfur trioxide-pyridine complex (577 mg, 3.63 mmol). The suspension was stirred overnight at room temperature. The suspension was evaporated to dryness and then resuspended in DCM. The solids were filtered off through a 0.45 μ nalgene filter. The filtrate was concentrated to afford an orange oil. This was taken up in DCM again and filtered through a 0.45 μ filter. The filtrate was concentrated to afford an orange oil. The crude material was taken to the next step without purification.

MS: 419 ES-, 303 ES+ ($C_{15}H_{23}N_4O_8S$, $C_{21}H_{20}P$)

EXAMPLE 7

(2S,5R)-2-(methoxymethyl)-7-oxo-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt



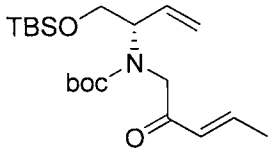
The title compound was prepared from (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-(methoxymethyl)-7-oxo-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 60**, 0.283 g, 0.47 mmol) following the procedure described for **Example 1**. The desired product was obtained after reverse phase HPLC purification (2-10% acetonitrile in water, Synergi Hydro RP, 19mm x 150mm, 5μm) as a white solid (40 mg, 26%).

Optical rotation: (0.1 g/dL, MeOH) = -170.

MS: 305 ES+ ($C_{11}H_{16}N_2O_6S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (s, 3H); 3.24 (m, 5H); 3.57 (m, 2H); 3.82 (m, 1H); 4.48 (m, 1H); 5.02 (m, 1H); 5.43 (m, 1H); 5.57 (m, 1H).

Intermediate 49: (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(2-oxopent-3-enyl)carbamate

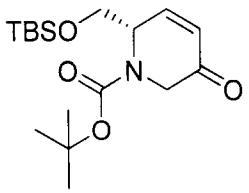


To a solution of (S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (**Intermediate 5**, 32.5 g, 80.73 mmol) in THF (400 mL) under nitrogen at 0 °C was added prop-1-enylmagnesium bromide (323 ml, 161.45 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 hour, then quenched with 400 mL 10% citric acid, diluted further with 100 mL water and extracted with ether. The organics were concentrated and the resulting oil was dissolved in ether and washed with water and brine. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (5%-20% ethyl acetate/hexanes) afforded the desired product as a colorless oil (27g, 87%).

MS: 384 ES+ ($C_{20}H_{37}NO_4Si$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.05 (2, 6H); 0.88 (s, 9H); 1.39-1.47 (m, 9H); 1.90 (m, 3H); 3.80 (m, 2H); 4.05-4.18 (m, 2H); 4.43-4.76 (m, 1H); 5.22 (m, 2H); 5.86 (m, 1H); 6.21 (m, 1H); 6.91 (m, 1H).

Intermediate 50: (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate



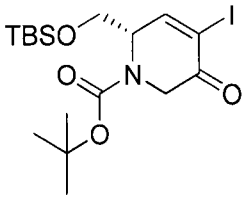
(S)-tert-butyl 1-(tert-butyldimethylsilyloxy)but-3-en-2-yl(2-oxopent-3-enyl)carbamate (**Intermediate 49**, 27.0 g, 70.39 mmol) was dissolved in toluene (650 ml). The solution was purged with nitrogen for 15 minutes before the addition of Hoveyda-Grubbs Catalyst 2nd Generation (0.885 g, 1.41 mmol). The reaction mixture was heated under nitrogen at 65 °C. After 2 hours LCMS showed complete formation of the product. The reaction mixture was concentrated under reduced pressure. Silica gel chrimatography (10%-35% ethyl acetate/hexanes) afforded the desired product as a solid (17.0g, 70%).

Optical Rotation: 0.1 g/dL, methylene chloride = -175

MS: 342 ES+ ($C_{17}H_{31}NO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.01 (s, 6H); 0.82 (s, 9H); 1.43 (s, 9H); 3.78-3.93 (m, 3H); 4.29 (m, 1H); 4.70 (m, 1H); 6.19 (dd, 1H); 7.15 (m, 1H).

Intermediate 51: (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-iodo-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate

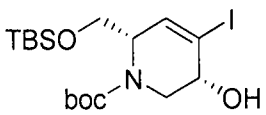


To a solution of (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 50**, 10 g, 29.28 mmol) and 4-dimethylaminopyridine (0.894 g, 7.32 mmol) in THF (100 mL)/water (100 mL) at room temperature was added potassium carbonate (3.24 g, 23.42 mmol) and iodine (8.92 g, 35.14 mmol). After stirring for 15 minutes, the reaction mixture was diluted with ether and washed with saturated sodium thiosulfate twice, then 5% citric acid and brine. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-15% ethyl acetate/hexanes) afforded the desired product as a tan oil (11.6 g, 85%).

MS: 468 ES+ ($C_{17}H_{30}INO_4Si$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H); 0.86 (s, 9H); 1.49 (s, 9H); 3.81 (m, 1H); 3.95 (m, 1H); 4.17 (m, 1H); 4.79 (m, 2H); 7.67 (m, 1H).

Intermediate 52: (2S,5R)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-iodo-5,6-dihydropyridine-1(2H)-carboxylate



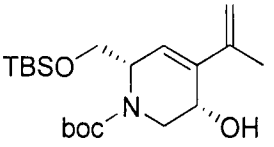
The title compound was prepared from (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-

iodo-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 51**, 10 g, 21.39 mmol) following the procedure described for **Intermediate 8**. The desired product was obtained as a colorless oil (8.87 g, 88%).

MS: 470 ES+ ($C_{17}H_{32}INO_4Si$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.03 (s, 6H); 0.86 (s, 9H); 1.40 (s, 9H); 2.87 (m, 1H); 3.65 (m, 2H); 3.79 (m, 1H); 4.21 (m, 2H); 5.74 (d, 1H); 6.44 (m, 1H).

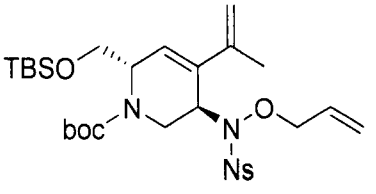
Intermediate 53: (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-(prop-1-en-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate



A solution of (2S,5R)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-iodo-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 52**, 8.57 g, 18.26 mmol), potassium trifluoro(prop-1-en-2-yl)borate (5.40 g, 36.51 mmol), potassium carbonate (3.11 mL, 54.77 mmol) and dichloro[1,1'-bis(di-t-butylphosphino)ferrocene]palladium(II) (1.190 g, 1.83 mmol) in dioxane (200 mL) and water (66.7 mL) at room temperature was purged with argon for 5 minutes then heated at 70 °C. The reaction mixture was concentrated onto silica gel. Silica gel chromatography (0%-20% ethyl acetate/hexanes) afforded a 2 to 1 mixture of desired product and starting material as a brown oil (5.36 g, 77%).

MS: 384 ES+ ($C_{20}H_{37}NO_4Si$)2

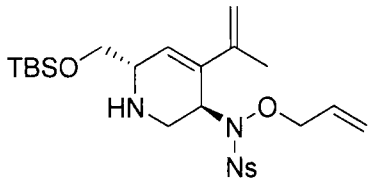
Intermediate 54: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-(prop-1-en-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate



The title compound was prepared from (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-(prop-1-en-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 53**, 3.86 g, 10.06 mmol) following the procedure described for **Intermediate 10**. The desired product was obtained as light yellow foam (3.25 g, 52%).

MS: 624 ES+ ($C_{29}H_{45}N_3O_8SSi$)

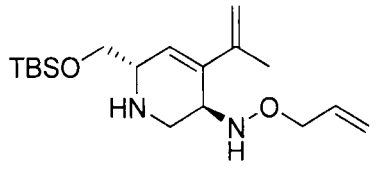
Intermediate 55: N-(allyloxy)-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-(prop-1-en-2-yl)-1,2,3,6-tetrahydropyridin-3-yl)-2-nitrobenzenesulfonamide



The title compound was prepared from (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-4-(prop-1-en-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 54**, 3.04 g, 4.87 mmol) following the procedure described for **Intermediate 21**. The desired produc twas obtained as an orange oil (2.53 g, 99%).

MS: 524 ES+ ($C_{24}H_{37}N_3O_6SSi$)

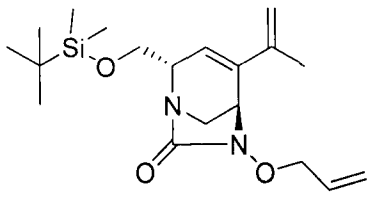
Intermediate 56: O-allyl-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-(prop-1-en-2-yl)-1,2,3,6-tetrahydropyridin-3-yl)hydroxylamine



The desired product was prepared from N-(allyloxy)-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)methyl)-4-(prop-1-en-2-yl)-1,2,3,6-tetrahydropyridin-3-yl)-2-nitrobenzenesulfonamide (**Intermediate 55**, 2.45 g, 4.68 mmol) following the procedure described for **Intermediate 22**. The desired produc twas obtained as yellow oil (1.19 g, 75%).

MS: 339 ES+ ($C_{18}H_{34}N_2O_2Si$)

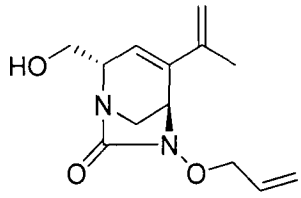
Intermediate 57: (2S,5R)-6-(allyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-7-one



The title compound was prepared from O-allyl-N-((3R,6S)-6-((tert-butyldimethylsilyloxy)-methyl)-4-(prop-1-en-2-yl)-1,2,3,6-tetrahydropyridin-3-yl)hydroxylamine (**Intermediate 56**, 1.22 g, 3.60 mmol) following the procedure described for **Intermediate 16**. The desired product was obtained as a light yellow oil (1.16 g, 88%).

MS: 365 ES+ ($C_{18}H_{32}N_2O_3Si$)

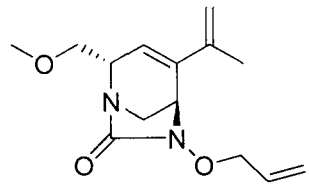
Intermediate 58: (2S,5R)-6-(allyloxy)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-7-one



The title compound was obtained from (2S,5R)-6-(allyloxy)-2-((tert-butyldimethylsilyloxy)-methyl)-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-7-one (**Intermediate 57**, 1.16 g, 3.18 mmol) following the procedure described for **Intermediate 14**. The desired produc twas obtained as a colorless oil (741 mg, 93%).

MS: 251 ES+ ($C_{13}H_{18}N_2O_3$)

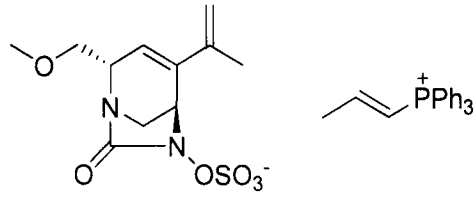
Intermediate 59: (2S,5R)-6-(allyloxy)-2-(methoxymethyl)-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-7-one



To a solution of (2S,5R)-6-(allyloxy)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-7-one (**Intermediate 58**, 0.289 g, 1.15 mmol) in DMF (10 mL) at 0 °C was added methyl iodide (0.435 mL, 6.93 mmol) followed by sodium hydride (60% in mineral oil) (0.051 g, 1.27 mmol). The reaction was stirred for 1.5 hours at 0 °C. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-50% ethyl acetate/hexanes) afforded the desired product as a pale yellow oil (233 mg, 76 %).

MS: 265 ES+ ($C_{14}H_{20}N_2O_3$)

Intermediate 60: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-(methoxymethyl)-7-oxo-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate

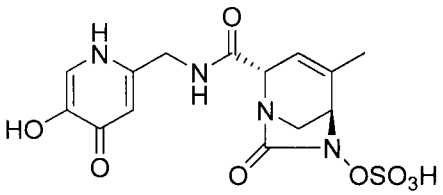


The title compound was prepared from 2S,5R)-6-(allyloxy)-2-(methoxymethyl)-4-(prop-1-en-2-yl)-1,6-diazabicyclo[3.2.1]oct-3-en-7-one (**Intermediate 59**, 233 mg, 0.88 mmol) following the procedure described for **Intermediate 17**. The desired product was obtained as an off-white foam (283 mg, 53%).

MS: 305 ES+, 303 ES+ ($C_{11}H_{16}N_2O_6S$, $C_{21}H_{20}P$)

EXAMPLE 8

(2S,5R)-2-((5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)methylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt

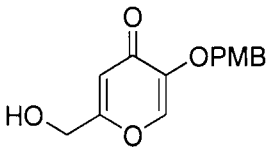


To a solution of (2S,5R)-2-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate (**Intermediate 68**, 58 mg, 0.09 mmol) in DCM (2 mL) at room temperature was added trifluoroacetic acid (0.505 mL, 6.55 mmol). The reaction mixture was stirred for 10 minutes and then concentrated. The resulting residue was dissolved in DCM and concentrated twice more. The product was purified twice by C18 RediSepRf Gold column (15.5 g) eluting with water manually using a syringe. The desired product was obtained after lyophilization as a white solid (3.4 mg, 9%).

MS: 401 ES+ ($C_{14}H_{16}N_4O_8S$)

^{1}H NMR (300 MHz, D_2O) δ: 1.93 (m, 3H); 3.25 (m, 1H); 3.58 (m, 1H); 4.20 (m, 1H); 4.50 (m, 2H); 4.59 (m, 1H); 5.67 (m, 1H); 6.76 (s, 1H); 7.77 (s, 1H).

Intermediate 61: 2-(hydroxymethyl)-5-(4-methoxybenzyloxy)-4H-pyran-4-one

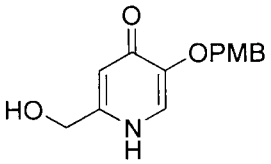


To a solution of 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one (**Alfa Aesar**, 5.11 g, 35.96 mmol) in DMF (70 mL) at room temperature was added potassium carbonate (9.94 g, 71.92 mmol) and 1-(chloromethyl)-4-methoxybenzene (5.86 mL, 43.15 mmol) dropwise. The reaction mixture was heated at 80 °C for 1 hour then concentrated. To the resulting slurry was added ice water. The precipitate was collected by filtration then triturated with ethyl acetate and filtered again. The title compound was obtained as a tan solid (6.44 g, 68%).

MS: 263 ES+ ($C_{14}H_{14}O_5$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.76 (s, 3H); 4.28 (s, 2H); 4.86 (s, 2H); 5.75 (m, 1H); 6.31 (s, 1H); 6.94 (m, 2H); 7.33 (m, 2H); 8.13 (s, 1H).

Intermediate 62: 2-(hydroxymethyl)-5-(4-methoxybenzyloxy)pyridin-4(1H)-one

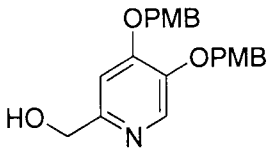


2-(hydroxymethyl)-5-(4-methoxybenzyloxy)-4H-pyran-4-one (**Intermediate 63**, 6.44 g, 24.56 mmol) and ammonia (7N in MeOH) (59.6 ml, 417.45 mmol) were combined in a pressure reactor vessel and heated at 90 °C for 5 hours. The reaction mixture was cooled overnight then concentrated. The solid was suspended in water then collected by filtration. The title compound was obtained as a brown solid (3.48 g, 54%).

MS: 262 ES+ ($C_{14}H_{15}NO_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.75 (s, 3H); 4.32 (s, 2H); 4.93 (s, 2H); 5.53 (m, 1H); 6.07 (m, 1H); 6.92 (m, 2H); 7.26 (m, 1H); 7.32 (m, 2H); 11.02 (m, 1H).

Intermediate 63: (4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methanol



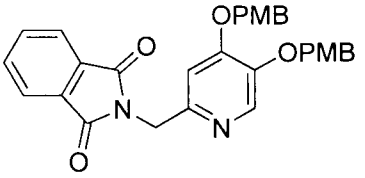
To a solution of 2-(hydroxymethyl)-5-(4-methoxybenzyloxy)pyridin-4(1H)-one (**Intermediate 62**, 3.48 g, 13.32 mmol) in DMF (100 mL) at room temperature was added 4-methoxybenzyl chloride (1.987 mL, 14.65 mmol) followed by potassium carbonate (2.273 mL, 39.96 mmol). The reaction mixture was stirred for 1 hour at room temperature then heated at 80 °C for 1.5 hours. The reaction mixture was cooled to room temperature, poured into water and extracted twice with ethyl acetate. The combined extracts were washed with water and brine. The ethyl acetate layer was concentrated to afford an oil. To the oil was added 1N HCl and a light brown solid crashed out. This was collected by filtration. The solid was taken up in ethyl acetate and washed with saturated sodium bicarbonate. The organics were dried over magnesium sulfate, filtered and concentrated to afford the title compound as a brown solid (2.62 g, 52%).

MS: 382 ES+ ($C_{22}H_{23}NO_5$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.74 (s, 3H); 3.76 (s, 3H); 4.42 (m, 2H); 5.05 (s, 2H); 5.12 (s,

2H); 5.27 (m, 1H); 6.93 (m, 4H); 7.17 (s, 1H); 7.32 (m, 4H); 8.07 (s, 1H).

Intermediate 64: 2-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methyl)isoindoline-1,3-dione

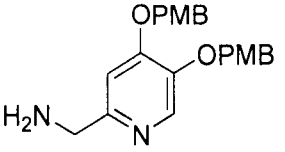


To a solution of (4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methanol (**Intermediate 63**, 1.5 g, 3.93 mmol), phthalimide (0.579 g, 3.93 mmol) and triphenylphosphine (1.028 g, 3.93 mmol) in THF (15 mL) at room temperature was added diisopropyl azodicarboxylate (2.091 mL, 10.62 mmol). The reaction was stirred at room temperature overnight then concentrated onto silica gel. Silica gel chromatography (0%-70% ethyl acetate) afforded the title compound as a light brown solid (1.1 g, 55%).

MS: 511 ES+ ($C_{30}H_{26}N_2O_6$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.73 (s, 3H); 3.74 (s, 3H); 4.78 (s, 2H); 5.01 (s, 2H); 5.10 (s, 2H); 6.89 (m, 4H); 7.16 (s, 1H); 7.32 (m, 4H); 7.89 (m, 4H); 8.01 (s, 1H).

Intermediate 65: (4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methanamine

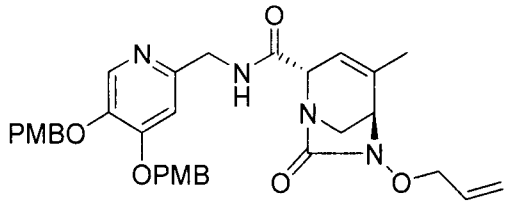


To a solution of 2-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methyl)isoindoline-1,3-dione (**Intermediate 64**, 1.1 g, 2.15 mmol) in chloroform (20 mL) and methanol (10 mL) at room temperature was added hydrazine hydrate (0.328 mL, 4.31 mmol). The reaction was stirred overnight at room temperature. Another 1 eq of hydrazine hydrate was added. After 4 hours the reaction mixture was filtered to remove the solids. The filtrate was concentrated to afford an orange oil. The oil was dissolved in methanol and ether was added to crash out more solids. This was repeated until no 2,3-dihydrophthalazine-1,4-dione by product remained. The title compound was obtained as an orange foam (0.82 g, 100%).

MS: 381 ES+ ($C_{22}H_{24}N_2O_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.66 (s, 2H); 3.74 (s, 3H); 3.76 (s, 3H); 5.03 (s, 2H); 5.11 (s, 2H); 6.92 (m, 4H); 7.20 (s, 1H); 7.35 (m, 4H); 8.05 (s, 1H).

Intermediate 66: (2S,5R)-6-(allyloxy)-N-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide

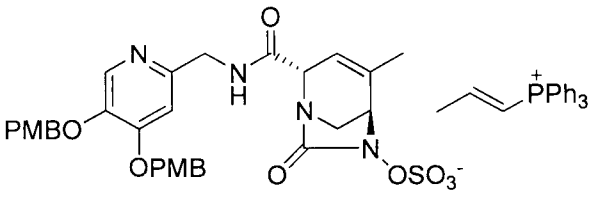


To a solution of (R)-6-(allyloxy)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxylic acid (**Intermediate 32**, 0.469 g, 1.97 mmol) in DMF (10 mL) at room temperature was added (4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methanamine (**Intermediate 65**, 0.824 g, 2.17 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.497 g, 3.94 mmol) and N,N-diisopropylethylamine (1.372 mL, 7.87 mmol). After 30 minutes the reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, brine, and 1/1 brine/water twice. The organics were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0%-50% ethyl acetate/hexanes) afforded the title compound as a light pink foam (0.427 g, 36%).

MS: 601 ES+ ($C_{33}H_{36}N_4O_7$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80 (m, 3H); 3.20 (m, 2H); 3.74 (s, 3H); 3.76 (s, 3H); 3.80 (m, 1H); 4.28 (m, 3H); 4.38 (m, 2H); 5.05 (s, 2H); 5.08 (s, 2H); 5.26 (m, 2H); 5.49 (m, 1H); 5.95 (m, 1H); 6.93 (m, 4H); 7.03 (s, 1H); 7.35 (m, 4H); 8.09 (s, 1H); 8.53 (m, 1H).

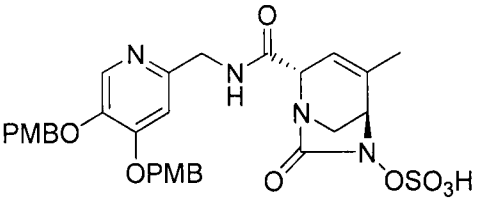
Intermediate 67: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate



To a solution of (2S,5R)-6-(allyloxy)-N-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (**Intermediate 66**, 0.427 g, 0.71 mmol) and acetic acid (0.081 mL, 1.42 mmol) (dried over sodium sulfate) in DCM (10 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (0.821 g, 0.71 mmol). The solution was stirred at room temperature for 1 hour. To the reaction mixture was added pyridine (10.00 mL) and sulfur trioxide-pyridine complex (0.679 g, 4.27 mmol). The suspension was stirred overnight at room temperature. The suspension was evaporated to dryness and then resuspended in DCM. The solids were filtered off through a 0.45 μ nalgene filter. The filtrate was concentrated and loaded onto a 24g RediSep silica column through a 0.45 μ nalgene filter. Silica gel chromatography (0%-100% acetone/DCM) afforded the title compound as a yellow foam (0.393 g, 59%).

MS: 639 ES-, 303 ES+ ($C_{30}H_{32}N_4O_{10}S$, $C_{21}H_{20}P$)

Intermediate 68: (2S,5R)-2-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt



The Dowex(R) 50WX8-100, ion-exchange resin (35 g) was conditioned by stirring for 3 hours in 2N sodium hydroxide (80 mL). The resin was then loaded into a glass column (2 x 12 inches) and washed with water until the pH was 7. It was then washed with (1/1) acetone/water (~500 mL), followed by water (~500 mL). (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-((4,5-bis(4-methoxybenzyloxy)pyridin-2-yl)methylcarbamoyl)-4-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 67**, 0.393 g, 0.42 mmol) was taken up in acetone (~2 mL) and diluted with water (~4 mL). The yellow solution was loaded on the resin

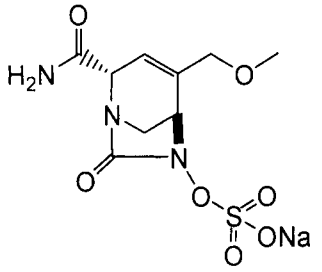
and eluted with water. The title compound was obtained after lyophilization as an off-white solid (124 mg, 45%).

MS: 641 ES+ ($C_{30}H_{32}N_4O_{10}S$)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.79 (m, 3H); 3.23 (m, 2H); 3.75 (m, 6H); 3.98 (m, 1H); 4.27 (m, 3H); 5.07 (m, 4H); 5.47 (m, 1H); 6.93 (m, 4H); 7.03 (s, 1H); 7.34 (m, 4H); 8.10 (s, 1H).

EXAMPLE 9

(2S,5R)-2-carbamoyl-4-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl hydrogen sulfate sodium salt

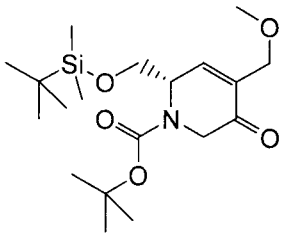


The Dowex(R) 50WX8-100, ion-exchange resin (10 g) was conditioned by stirring for 3 hours in 2N sodium hydroxide (30 mL). The resin was then loaded into a cartridge and washed with water until the pH was 7. It was then washed with (1/1) acetone/water (~100 mL), followed by water (~100 mL). (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-4-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 76**, 131 mg, mmol) was taken up in water (~1 mL) and minimum acetnitrile. The yellow solution was loaded on the resin and washed through with water. The title compound was obtained after lyophilization as an off-white solid (38 mg, 50%).

MS: 308 ES+ ($C_9H_{12}N_3NaO_7S$)

^{1}H NMR (300 MHz, D_2O) δ: 3.43 (d, 1H); 3.53 (s, 3H); 3.59 (m, 1H); 3.80 (m, 1H); 4.24 (q, 2H); 4.45 (m, 1H); 6.11 (m, 1H).

Intermediate 69: (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-(methoxymethyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate

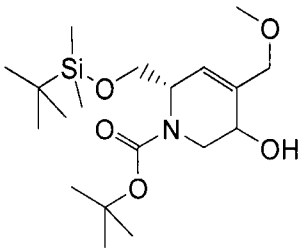


To a stirred solution of (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-(hydroxymethyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (17.37 g, 46.75 mmol) in DCM (480 mL) was added N1,N1,N8,N8-tetramethylnaphthalene-1,8-diamine (60.1 g, 280.51 mmol). Then it was cooled to 0°C and trimethyloxonium tetrafluoroborate (20.74 g, 140.25 mmol) was added. It was then stirred at rt for 6h. Then it was concentrated under reduced pressure. The residue was then taken up in 100 mL Et_2O and filtered, washed with 400 mL Et_2O. The organic layer was then washed with 10% citric acid, aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated to afford the desired product (16.73 g, 93 %) as an oil.

MS: 386 ES+ ($C_{19}H_{35}NO_5Si$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.01 (s, 6H); 0.81 (s, 9H); 1.42 (s, 9H); 3.28 (s, 3H); 3.91 (m, 5H); 4.33 (d, 1H); 4.78 (m, 1H); 7.01 (s, 1H).

Intermediate 70: (2S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate



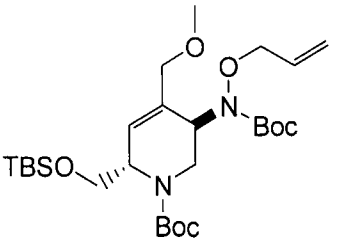
(S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-(methoxymethyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate) (**Intermediate 69**, crude, 16.73 g, 43.39 mmol) was dissolved in MeOH (100 mL), cooled to 0°C and $CeCl_3$ (10.69g, 43.39 mmol) was added to give a solution. Then $NaBH_4$ (1.642 g, 43.39 mmol) was added slowly as solid, and the mixture was stirred from 0°C to rt for 30 min. The volatile solvent was removed. The white solid was redissolved in 200 mL EtOAc and washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered

and concentrated. The residue was purified by silica gel column (0-100% EA/Hex) to afford 13.78 g, 82 % as an colorless oil.

MS: 410 ES+ ($C_{19}H_{37}NO_5Si + Na^+$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H); 0.89 (s, 9H); 1.46 (s, 9H); 3.10 (m, 1H); 3.36 (s, 3H); 3.68 (m,1H); 3.72 (m, 1H); 4.11 (m, 2H); 4.24 (m, 2H); 4.39 (m, 1H); 5.75 (m, 1H).

Intermediate 71: (2S,5R)-tert-butyl 5-(allyloxy(tert-butoxycarbonyl)amino)-2-((tert-butyldimethylsilyloxy)methyl)-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate



To a stirred solution of (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 70**, 13.78 g, 35.55 mmol) in DCM (200 mL) at 0°C, pyridine (14.38 mL, 177.77 mmol) and N,N-dimethylpyridin-4-amine (217 mg, 1.78 mmol) was added. Then methanesulfonic anhydride (9.29 g, 53.33 mmol) was added. The mixture was then stirred from 0°C to rt for 2 hrs. It was diluted with DCM (200 mL) and washed with brine, dried over $MgSO_4$, filtered and concentrated to give (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-(methoxymethyl)-5-(methylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (crude, 16.9 g) as an pale yellow oil. It was used directly for the next step.

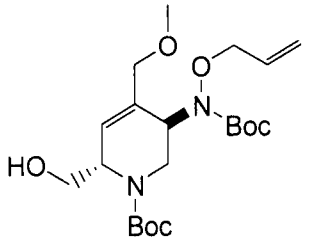
To a stirred solution of tert-butyl allyloxycarbamate (7.39 g, 42.66 mmol) in DMF (150 mL) at rt, potassium 2-methylpropan-2-olate (42.66 mL, 42.66 mmol) was added and gave a purple solution. After 30 min at rt, the mixture was cooled to 0°C and (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-4-(methoxymethyl)-5-(methylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (crude, 16.55 g, 35.55 mmol) in 50.0 mL DMF was added. The mixture was then warmed up to rt for 1h. It was then diluted with ethyl acetate (200 mL) and washed aqueous sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated to give a residue which contains some starting material. The crude was purified on a silica gel column yielding a

colorless oil. (19.3 g). ^{1}HNMR shows still a mixture (with hydroxyamine starting material). It was used directly in TBS deprotection.

MS: 565 ES+ ($C_{27}H_{50}N_2O_7Si + Na^+$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H); 0.89 (s, 9H); 1.47 (s, 9H); 1.52 (s, 9H); 3.14 (m, 1H); 3.31 (s, 3H); 3.72 (m, 3H); 4.15 (m, 3H); 4.44 (m, 3H); 5.28 (m, 2H); 5.97 (m, 2H).

Intermediate 72: (2S,5R)-tert-butyl 5-(allyloxy(tert-butoxycarbonyl)amino)-2-(hydroxymethyl)-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate



To a stirred solution of (2S,5R)-tert-butyl 5-(allyloxy(tert-butoxycarbonyl)amino)-2-((tert-butyldimethylsilyloxy)methyl)-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 71**, 35.55 mmol) in THF (100 mL) at 0°C, TBAF (39.11 mL, 39.11 mmol) was added. After 1hr at 0°C, it was then concentrated to give a residue which was purified by silica gel column (0-100% EA/Hex) to give the desired product (8.82 g, 57.9 % over 3 steps) as a colorless oil.

MS: 451 ES+ ($C_{21}H_{36}N_2O_7 + Na^+$)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H); 1.52 (s, 9H); 3.14 (dd, 1H); 3.34 (s, 3H); 3.71 (m, 3H); 3.98 (d, 1H), 4.18 (m, 2H); 4.40 (m, 2H); 4.67 (m, 1H); 5.20 (m, 2H); 5.79 (m, 1H); 5.97 (s, 1H).

Intermediate 73: (2S,5R)-tert-butyl 5-(allyloxy(tert-butoxycarbonyl)amino)-2-carbamoyl-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate

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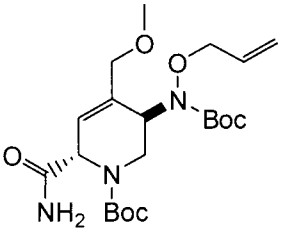


Stock oxidation solution: ~480 mg conc. HNO_3 and ~160 mg $Na_2Cr_2O_7$-$2H_2O$ was dissolved in 32 mL H_2O at rt.

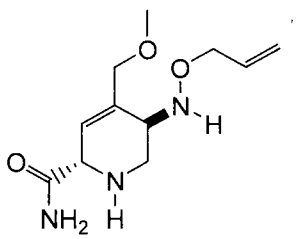
To a stirred solution of (2S,5R)-tert-butyl 5-(allyloxy(tert-butoxycarbonyl)amino)-2-(hydroxymethyl)-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 72**, 8.82 g, 20.58 mmol) in 100 mL MeCN at 0°C, was added sodium periodate (19.37 g, 90.56 mmol). Then 12 mL of the stock oxidation solution was added. The suspension was then stirred at rt for 2d. An additional 16 mL the above stock solution was added and stired for 2 more days. The mixture was diluted with 150 mL ethyl acetate, 50 mL 1M pH 7 buffer, and 50 mL 2M $NaHSO_3$. The aqueous was extracted with 20 mL ethyl acetate. The ethyl acetate layer was then washed with brine. The aqeous layer was checked by LCMS and found containing desired carboxylic acid. The aqueous layer was then extracted with 50 mL ethyl acetate and washed with brine. The combined organic layers was dried over $MgSO_4$, filtered and concentrated to afford a yellow dry film, (crude 7.11 g, 78 %) which was used directly without further purification.

To a stirred solution of (2S,5R)-5-(allyloxy(tert-butoxycarbonyl)amino)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)-1,2,5,6-tetrahydropyridine-2-carboxylic acid (crude, 7.11 g, 16.07 mmol), ammonium chloride (1.719 g, 32.14 mmol), HATU (12.22 g, 32.14 mmol) in DMF (50.0 mL) at rt, was added DIPEA (8.31 g, 64.27 mmol). After stirring at rt for 1hr, 100 mL EtOAc was added. The organic layer was washed with water, brine. The residue was purified by silica gel coulmn (0-100% Hex/EA) to afford the desired product (3.07 g, 43.3%) as an off-white solid.

MS: 442 ES+ ($C_{21}H_{35}N_3O_7$)

^{1}H NMR (300 MHz, CD_3OD) δ: 1.47 (s, 9H); 1.52 (s, 9H); 3.17 (d, 1H); 3.34 (s, 3H); 4.04 (m, 1H); 4.12 (m, 4H); 4.44 (m, 2H); 5.21 (m, 2H); 5.77 (m, 1H); 6.22 (s, 1H).

Intermediate 74: (2S,5R)-5-(allyloxyamino)-4-(methoxymethyl)-1,2,5,6-tetrahydropyridine-2-carboxamide

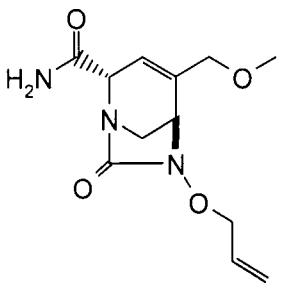


(2S,5R)-tert-butyl 5-(allyloxy(tert-butoxycarbonyl)amino)-2-carbamoyl-4-(methoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 73**, 3.07 g, 6.95 mmol) was dissolved in 20 mL DCM. Then 5.36 mL TFA was added dropwise at 0°C. The mixture was stirred at rt for 3h. The olvent was removed in vacuo and co-evaporated twice with 5 mL MeOH. The residue was dissolved in MeOH (10 mL) and amonium hydroxide (30% in water) was added until it was basic. The mixture was rotovapored at rt and the residue was freeze-dried over night to give a solid. It was dissolved in DCM and purified on silica gel eluting with 0-100% MeOH/DCM to give a off-white solid (1.12 g, 66.8 %).

MS: 242 ES+ ($C_{11}H_{19}N_3O_3$)

^{1}H NMR (300 MHz, CD_3OD) δ: 3.31 (s, 3H); 3.55 (m, 3H); 4.05 (m, 4H); 4.58 (m, 1H); 5.20 (m, 2H); 5.96 (m, 2H).

Intermediate 75: (2S,5R)-6-(allyloxy)-4-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide



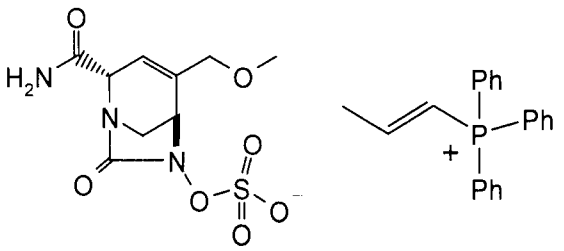
To a stirred solution of (2S,5R)-5-(allyloxyamino)-4-(methoxymethyl)-1,2,5,6-tetrahydropyridine-2-carboxamide (**Intermediate 74**, 1.12 g, 4.64 mmol) in acetonitrile (100 mL), N-ethyl-N-isopropylpropan-2-amine (4.04 mL, 3.00 g, 23.21 mmol) was added, then triphosgene (551 mg, 1.86 mmol) in 20 mL acetonitrile was added slowly via syringe pump over 4 h at 0°C. It was stirred from 0°C to rt overnight. The solution was concentrated to give a residue, which was then taken up in 50 mL EtOAc and washed with brine, dried over $MgSO_4$,

filtered and concentrated. The residue was purified on a silica gel column eluting with 0-100% ethyl acetate/hexanes gave a yellow oil (420 mg, 34%).

MS: 268 ES+ ($C_{12}H_{17}N_3O_4$)

^{1}H NMR (300 MHz, CD_2Cl_2) δ: 3.03 (d, 1H); 3.28 (s, 3H); 3.40 (m, 2H); 3.95 (m, 3H); 4.38 (m, 2H); 5.30 (m, 2H); 5.98 (m, 2H); 6.83 (bs, 2H).

Intermediate 76: (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-4-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate

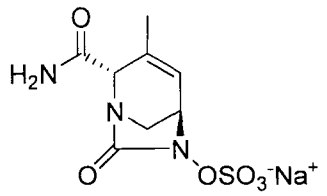


To a solution of (2S,5R)-6-(allyloxy)-4-(methoxymethyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-ene-2-carboxamide (**Intermediate 75**, 120 mg, 0.45 mmol) and acetic acid (0.051 mL, 0.90 mmol) (dried over sodium sulfate) in DCM (4.0 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (519 mg, 0.45 mmol). The solution was stirred at room temperature for 1 hour. To the reaction mixture was added pyridine (2.0 mL) and sulfur trioxide-pyridine complex (429 mg, 2.69 mmol). The suspension was stirred overnight at room temperature. The suspension was evaporated to dryness and then resuspended in DCM. The solids were filtered off through a 0.45 μ nalgene filter. The filtrate was concentrated and loaded onto a 24g RediSep silica gel column through a 0.45 μ nalgene filter. Silica gel chromatography (0%-100% acetone/DCM) afforded the title compound as a yellow foam (0.131 g, 48%).

MS: 304 ES+ ($C_{30}H_{32}N_3O_7PS$, $C_{21}H_{20}P$)

EXAMPLE 10

(2S,5R)-2-carbamoyl-3-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sodium sulfate



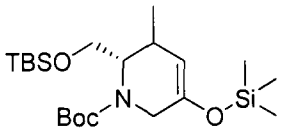
The Dowex(R) 50WX8-100, ion-exchange resin (25 g, 0.33 mmol) was conditioned by stirring for 3 hours in 2N sodium hydroxide (61 mL, 0.33 mmol). The resin was then loaded into a cartridge and washed with water until the pH was 7. It was then washed with (1/1) acetone/water, followed by water. (E)-triphenyl(prop-1-enyl)phosphonium (2S,5R)-2-carbamoyl-3-methyl-7-oxo-1,6-diazabicyclo[3.2.1]oct-3-en-6-yl sulfate (**Intermediate 87**, 68 mg, 0.12 mmol) was taken up in water. Acetone was added dropwise until everything was in solution. The yellow solution was loaded on the resin and washed through with water. The fractions containing desired product were combined and lyophilized (25mg, 79%) yielding a white solid.

Optical rotation: (0.1 g/dL, MeOH) = -287.

MS: 276 ES- ($C_8H_{10}N_3O_6SNa$)

^{1}H NMR (300 MHz, DEUTERIUM OXIDE) δ: 1.76 (dd, *J*=1.41, 0.85 Hz, 3 H) 3.40 - 3.49 (m, 1 H) 3.50 - 3.58 (m, 1 H) 4.27 (dd, *J*=5.09, 2.45 Hz, 1 H) 4.44 (s, 1 H) 6.23 - 6.31 (m, 1 H).

Intermediate 77: (6S)-tert-butyl 6-((tert-butyldimethylsilyloxy)methyl)-5-methyl-3-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate



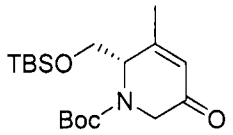
Methyllithium in Et_2O (73.2 mL, 117.12 mmol) was added dropwise over 20 min. to a suspension of copper(I) iodide (11.15 g, 58.56 mmol) in Et_2O (160 mL) and stirred at 0°C under nitrogen. After 45 min (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (10 g, 29.28 mmol) in Et_2O (20 mL) was added dropwise and continued stirring for 45 min. TMs-Cl in THF (58.6 mL, 58.56 mmol) was added, followed by triethylamine (8.16 mL, 58.56 mmol). The resultant mixture was stirred at rt for 2h, diluted with

ethylacetate washed with ice-cold sat. $NaHCO_3$ (3x) and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to obtain the desired product as a crude yellow oil (~12.58g, 29.27 mmol).

MS: 330 ES+ ($C_{21}H_{43}NO_4Si_2$)

1H NMR (300 MHz, CHLOROFORM-*d*) δ: 0.05 - 0.08 (m, 6 H) 0.21 (br. s., 9 H) 0.89 (br. s., 9 H) 1.04 (d, *J*=6.40 Hz, 2 H) 1.48 (s, 9 H) 2.34 (br. s., 1 H) 3.42 (br. s., 2 H) 3.54 (dd, *J*=7.44, 3.67 Hz, 1 H) 3.91 - 4.04 (m, 1 H) 4.07 - 4.20 (m, 1 H) 4.87 (br. s., 1 H)

Intermediate 78: (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-3-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate

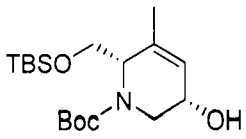


The crude (6S)-tert-butyl 6-((tert-butyldimethylsilyloxy)methyl)-5-methyl-3-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 77**, 12.58 g, 29.27 mmol) in 8 mL ACN was stirred at rt with $Pd(OAc)_2$ (6.57 g, 29.27 mmol) for 2 days. The mixture was diluted with 160 mL EtOAc, filtered through celite, concentrated in vacuo and subjected to flash chromatography (220g, 0-30% EA/Hex) to obtain the desired product (6.07 g, 58.3 %) (over two steps) as a beige solid.

MS: 256 ES+ ($C_{18}H_{33}NO_4Si$)

1H NMR (300 MHz, CHLOROFORM-*d*) δ -0.02 - 0.07 (m, 6 H) 0.80 - 0.91 (m, 9 H) 1.49 (s, 9 H) 2.04 (d, *J*=1.13 Hz, 3 H) 3.69 - 4.06 (m, 3 H) 4.32 - 4.73 (m, 2 H) 6.08 (s, 1 H)

Intermediate 79: (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-3-methyl-5,6-dihydropyridine-1(2H)-carboxylate

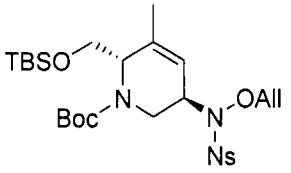


To a stirred solution of cerium(III) chloride heptahydrate (6.36 g, 17.07 mmol) and (S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-3-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 78**, 6.07 g, 17.07 mmol) in MeOH (100 mL) at 0°C, sodium tetrahydroborate (0.646 g, 17.07 mmol) was added as a solid. The mixture was stirred at ambient temp for 1h. The mixture was concentrated and diluted with NH_4Cl(aq), H_2O and extracted with ether. The ether layer was separated and washed with brine, dried over Na_2SO_4, filtered and concentrated to give the desired product (5.48 g, 90 %) as a yellow oil.

MS: 258 ES+ ($C_{18}H_{35}NO_4Si$)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ: 0.06 (s, 6 H) 0.78 - 0.94 (m, 9 H) 1.38 - 1.50 (m, 9 H) 1.56 (br. s., 1 H) 1.78 (s, 3 H) 2.90 - 3.39 (m, 1 H) 3.67 - 4.28 (m, 5 H) 5.80 (br. s., 1 H).

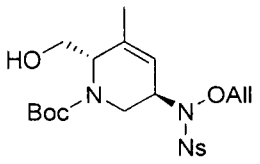
Intermediate 80: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-3-methyl-5,6-dihydropyridine-1(2H)-carboxylate



To a stirred suspension of (2S,5S)-tert-butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-hydroxy-3-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 79**, 5.48 g, 15.33 mmol), N-(allyloxy)-2-nitrobenzenesulfonamide (7.92 g, 30.65 mmol) and triphenylphosphine (12.06 g, 45.98 mmol) in toluene (20 mL) was cooled in an ice-bath and added dropwise (E)-diisopropyl diazene-1,2-dicarboxylate (8.91 ml, 45.98 mmol). Reaction was let warm up to rt and continued to stirr at rt for 2h. The reacation mixture was evaporated and the crude product was loaded onto silica gel, purified via flash chromatography (750g, 0-50%) to obtain the desired product (7.05 g, 77 %) as a yellow oil.

MS: 598 ES+ ($C_{27}H_{43}N_3O_8SSi$)

Intermediate 81: (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-(hydroxymethyl)-3-methyl-5,6-dihydropyridine-1(2H)-carboxylate

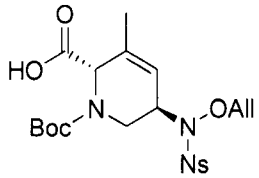


(2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-((tert-butyldimethylsilyloxy)methyl)-3-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 80**, 7.05 g, 11.79 mmol) in THF (100 mL) was charged with nitrogen and cooled in an ice-bath. Tetrabutylammonium fluoride in THF (14.15 mL, 14.15 mmol) was added to the solution and stirred at rt. The reacation mixture was evaporated and the crude product was loaded onto silica and purified via flash chroamtography (30-100%EA/Hexanes, 40g column), to obtain the desired product (4.52 g, 79 %) as a pale yellow foam.

MS: 484 ES+ ($C_{21}H_{29}N_3O_8S$)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ: 1.43 (br. s., 9 H) 1.80 (br. s., 3 H) 3.35 (br. s., 1 H) 3.73 (d, *J*=6.22 Hz, 1 H) 3.88 (br. s., 1 H) 4.35 (br. s., 5 H) 5.15 - 5.29 (m, 2 H) 5.45 (s, 1 H) 5.77 (br. s., 1 H) 7.61 (d, *J*=7.35 Hz, 1 H) 7.76 (dd, *J*=12.62, 7.54 Hz, 2 H) 8.13 (d, *J*=7.72 Hz, 1 H)

Intermediate 82: (2S,5R)-5-(N-(allyloxy)-2-nitrophenylsulfonamido)-1-(tert-butoxycarbonyl)-3-methyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid

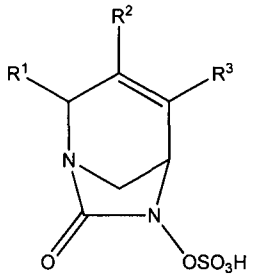


To a solution of periodic acid (4.10 g, 17.99 mmol) in wet acetonitrile (25mL) (0.75% water by volume) at room temperature was added chromium(VI) oxide (0.490 g, 4.90 mmol). The mixture was stirred until complete dissolution was achieved.

To a solution of (2S,5R)-tert-butyl 5-(N-(allyloxy)-2-nitrophenylsulfonamido)-2-(hydroxymethyl)-3-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**Intermediate 81**, 4.52 g, 9.35 mmol) in wet acetonitrile (25mL) (0.75% by volume) at 0 °C was added dropwise the previously formed periodic acid/chromium oxide solution. The reaction was stirred o/n at rt. The reaction mixture was diluted with $CHCl_3$ and washed with conc. citric acid/water and then with brine (2x). The organics were dried over magnesium sulfate, filtered and concentrated to obtain

CLAIMS

1. A compound according to formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is –CONR'R'', or -CN;

R^2 and R^3 are independently selected from H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, -CONR'R'', or $C(O)_2R'$; wherein the alkyl, alkenyl, cycloalkyl, and alkoxy represented by R^2 or R^3 are independently and optionally substituted by one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', 5-7 membered heterocycle, -C(O)NR'R'' or -NR'C(O)R''; and

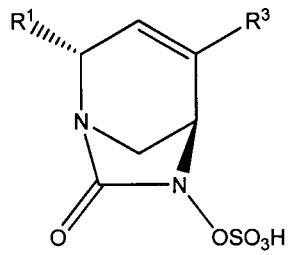
each R' and R'' are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 5 to 6 membered heterocyclyl or a 5 to 6 membered heteroaryl; wherein each alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally and independently substituted with one or more halo, -CN, -OH, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -C(O)(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkoxy), -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 5-7 membered heterocyclyl or a 5-7 membered heteroaryl;

provided that R^2 and R^3 are not both hydrogen; and when R^1 is –C(O)NR'R'', then neither of R^2 or R^3 is –C(O)NR'R''.

2. The compound of Claim 1, according to formula (III):

methyl.

7. The compound of claim 1, according to formula (IV):



or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein

R^3 is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, or -CONR'R'', each of which is optionally and independently substituted with one or more substituent selected from the group consisting of halo, -CN, -OH, C_1-C_3 alkyl, cyclopropyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -NR'R'', a siderophore, -C(O)NR'R'' and -NR'C(O)R''; and

each R' and R'' is independently selected from H and C_1-C_3 alkyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein

R^3 is methyl, ethyl, isopropyl, cyclopropyl, $-CONH_2$, -CONH(C_1-C_3 alkyl), or -CON(C_1-C_3 alkyl)$_2$, each of which is optionally and independently substituted with one or more group selected from -OH, C_1-C_3 alkyl, C_1-C_3 alkoxy, -NR'R'', C(O)NR'R'' and -NR'C(O)R''; and

each R' and R'' is independently selected from H and C_1-C_3 alkyl.

10. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein

R^3 is C_1-C_3 alkyl, cyclopropyl, –CONR'R'', wherein each alkyl, and cyclopropyl is optionally and independently substituted with one or more -OH, C_1-C_3 alkoxy, $-NH_2$, or