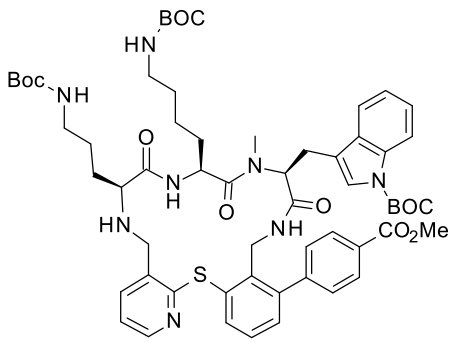
palladium impurities in the final product that are difficult to remove. Similarly, the use of high amounts of boronic acid results in the formation of organic impurities. Furthermore, the process disclosed in WO2019206853 involves the use of the toxic solvent dioxane, and relies on chromatography to purify certain intermediates, as well as the final product.

In summary, the process for making the compound of formula (I) as described in WO2019206853 is not well suited for an industrial scale synthesis of said compound of formula (I). Accordingly, there is a high unmet need for a new process for manufacturing the compound of formula (I), in order to provide patients with this new treatment option for infections with *Acinetobacter baumannii* and resulting diseases.

Summary

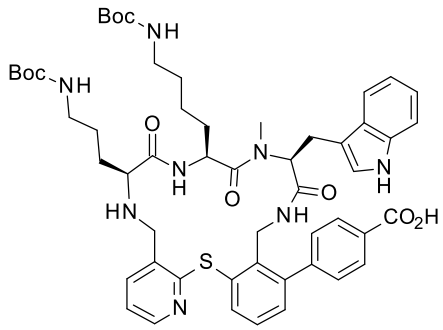
The present disclosure provides an improved process for manufacturing the compound of formula (I), which overcomes the problems outlined above. The present disclosure also provides certain synthetic intermediates that are useful in the new process.

In one aspect, the present disclosure provides a compound, which is tert-butyl 3-[[(11S,14S,17S)-14-[4-(tert-butoxycarbonylamino)butyl]-11-[3-(tert-butoxycarbonylamino)propyl]-22-(4-methoxycarbonylphenyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3,5,7,21,23-hexaen-17-yl]methyl]indole-1-carboxylate (**3**), or a salt thereof



3 .

In another aspect, the present disclosure provides a compound, which is 4-[(11S,14S,17S)-14-[4-(tert-butoxycarbonylamino)butyl]-11-[3-(tert-butoxycarbonylamino)propyl]-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3,5,7,21,23-hexaen-22-yl]benzoic acid (**4**), or a salt thereof

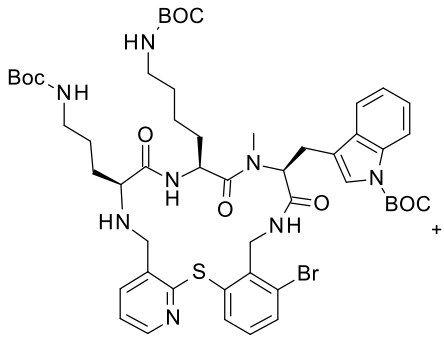


4

.

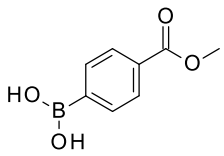
In another aspect, the present disclosure provides a process for manufacturing compound **3** as described herein, or a salt thereof, comprising:

(a) reacting aryl bromide **1**



1

with (4-carbomethoxyphenyl)boronic acid (**2**)



2

in the presence of a palladium catalyst and a base in an aromatic solvent, to afford said compound **3**; wherein said palladium catalyst is selected from:

i) a preformed catalyst selected from $Pd(PPh_3)_4$, $Pd(L^1)_2$, $[Pd(L^1)XCl]$, $[Pd(L^1)X]$trifluoromethanesulfonate, $[Pd(L^1)$(2-(2′-amino-1,1′-biphenyl)Cl]; $[Pd(L^1)$(2-(2′-amino-1,1′-biphenyl)]methanesulfonate, $[Pd(L^1)$(2-(2′-methylamino-1,1′-biphenyl)]methanesulfonate, $[Pd(L^1)$(2-(2-aminoethyl)phenyl)Cl], $Pd(L^2)Cl_2$, $Pd(L^2)_2Cl_2$, and $[PdI(L^3)]_2$; wherein X is selected from allyl, 2-butenyl, 2-methylallyl, 1-phenylallyl, *p-tert*-butylindenyl; L^1 is selected from PBu_3, AmPhos, CPhos, RuPhos, and SPhos; L^2 is selected from $PtBu_3$, AmPhos, $PtBu_2Bu$, $PtBu_2Ph$, $PtBu_2$-*p*-$C_6H_4CF_3)_2$, dppf, dcypf, dippf, and dtbpf; and L^3 is selected from $PtBu_3$, AmPhos; and

ii) a catalyst that is formed *in situ* from:

iia) a palladium source selected from palladium bis(dibenzylideneacetone) ($Pd(dba)_2$), ($Pd_2(dba)_3$), bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), palladium acetate ($Pd(OAc)_2$, palladium trifluoracetate ($Pd(TFA)_2$), palladium chloride ($PdCl_2$), palladium bromide ($PdBr_2$),palladium iodide (PdI_2), palladium bis acetylacetonate ($Pd(acac)_2$), ($Pd(PPh_3)_4$), bis(acetonitrile)-palladium(II) dichloride ($PdCl_2(CH_3CN)_2$), cyclopentadienyl allyl palladium, allylpalladium(II) chloride dimer ($Pd(allyl)Cl)_2$), (2-butenyl)chloropalladium dimer, (2-methylallyl) palladium(II) chloride dimer, palladium(1-phenylallyl)chloride dimer,(*p-tert*-butylindenyl) palladium(II) chloride dimer, di-μ-chlorobis[2′-(amino-*N*)[1,1′-biphenyl]-2-yl-*C*]dipalladium(II), di-μ-mesylbis[2′-(amino-N)[1,1′-biphenyl]-2-yl-C]dipalladium(II), di-μ-mesylbis[2′-(methylamino-N)[1,1′-biphenyl]-2-yl-C]dipalladium(II), and di-μ-chlorobis[2-[(dimethylamino)methyl]phenyl-C,N]dipalladium(II); and

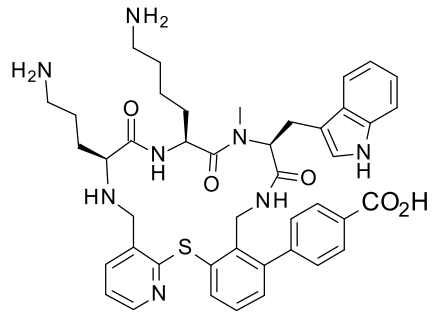
iib) a ligand selected from mono- and diphosphines, in particular a ligand selected from $PtBu_3$, PAd_3, AmPhos, cataCXiumA, $PtBu_2Bu$, $PtBu_2Ph$, $PtBu_2$-*p*-$C_6H_4CF_3$, cataCXium POMeCy, CPhos, RuPhos, SPhos, dppf, dcypf, dippf, and dtbpf; and

said base is selected from inorganic bases and alcoholates, preferably wherein said base is selected from Na_2CO_3, $Ba(OH)_2$, K_3PO_4, Cs_2CO_3, K_2CO_3, TlOH, KF, CsF, Bu_4F, and NaOH, more preferably wherein said base is K_3PO_4 or K_2CO_3.

In another aspect, the present disclosure provides a process for manufacturing compound **4** as described herein, or a salt thereof, comprising the process as described herein, and further comprising:

(c) reacting compound **3** as described herein with 2 to 10 equivalents, preferably 3 to 8 equivalents, more preferably 4 to 7 equivalents, in particular 7 equivalents of sodium hydroxide to afford said compound **4**, wherein said sodium hydroxide is added as a 5% w/w to 30% w/w, preferably 10% w/w to 20% w/w, in particular a 16% w/w aqueous solution to a solution of compound **3** in an alcoholic solvent or a mixture of water and an alcoholic solvent.

In another aspect, the present disclosure provides a process for manufacturing the compound of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

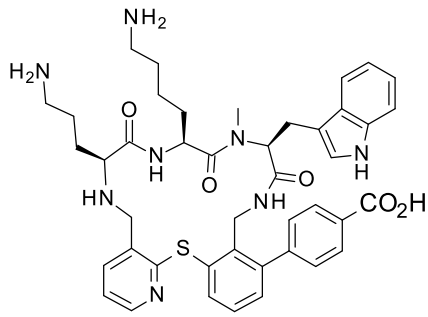
comprising the process as described herein, and further comprising:

(e) reacting compound **4** as described herein with an acid, preferably with hydrochloric acid, to afford said compound of formula (I).

In another aspect, the present disclosure provides compound **3** as described herein, or a salt thereof, when manufactured according to the process as described herein.

In another aspect, the present disclosure provides compound **4** as described herein, or a salt thereof, when manufactured according to the process as described herein.

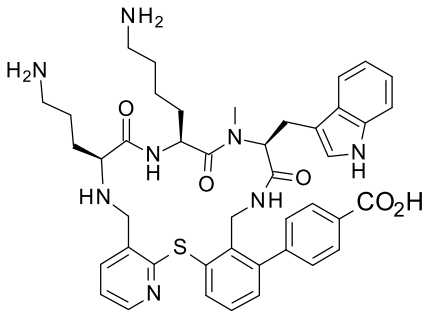
In another aspect, the present disclosure provides compound of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

when manufactured according to the process as described herein.

In another aspect, the present disclosure provides use of the process as described herein in the manufacture of the compound of formula (I),



(I)

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides use of compound **3** as described herein in the manufacture of the compound of formula (I).

In another aspect, the present disclosure provides use of compound **4** as described herein in the manufacture of the compound of formula (I).

Detailed Description of the Invention

Definitions

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims and the abstract), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims and the abstract), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The term “palladium catalyst” as used herein refers to any palladium catalyst that enables the reaction of aryl bromide **1** as described herein with (4-carbomethoxyphenyl)boronic acid (**2**) to afford compound **3** as defined herein on an industrial scale. The palladium catalyzed reaction according to the invention requires a zero valent palladium species