JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

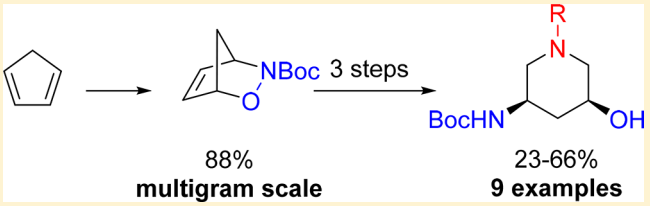
Modular Access to N-Substituted *cis* 5-Amino-3-hydroxypiperidines

Paola Gordillo Guerra, Paolo Clerici, and Laurent Micouin*

Laboratoire de Chimie et de Biochimie Pharmacologiques et Toxicologiques, Faculté des Sciences Fondamentales et Bio-médicales, UMR 8601, CNRS-Paris Descartes University, 45 rue des Saints Pères, 75006 Paris, France

Supporting Information

ABSTRACT: A sequence of oxidative cleavage/reductive amination/reductive cleavage enables the preparation of N-substituted *cis* 5-amino-3-hydroxypiperidines from a readily available bicyclic adduct. This new route provides straightforward and versatile access to drug-relevant scaffolds or fragments.



The 3-aminopiperidine scaffold of type A can be found in a variety of approved drugs, such as tofacitinib,[1] ibrutinib,[2] alogtliptin,[3] linagliptin,[4] palonasetron,[5] and also in many biologically active compounds of natural or synthetic origin (Figure 1).[6] An interesting subclass of this general motif

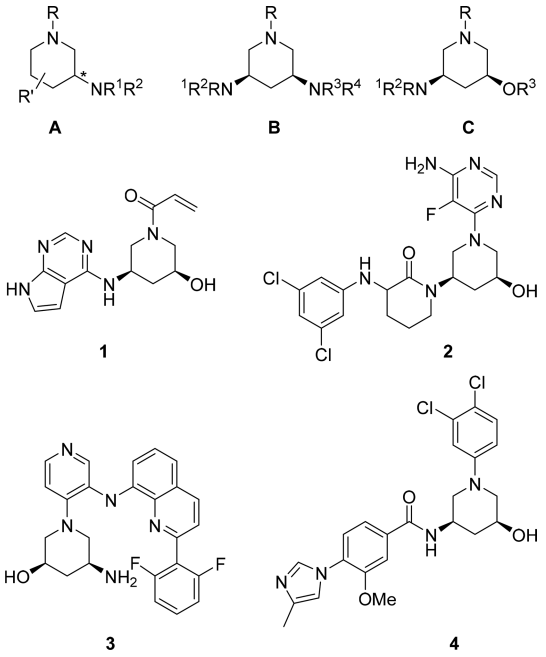
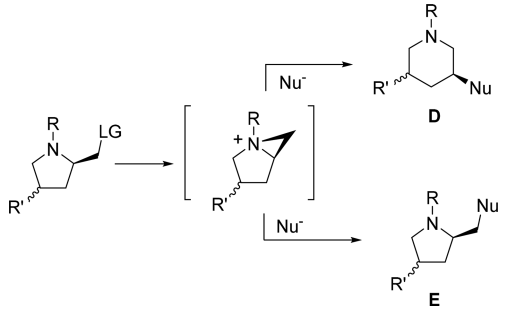


Figure 1. Aminopiperidine scaffolds and selected examples of biologically active compounds.

consists of 5-substituted 3-aminopiperidines, such as *cis* or *trans* 3,5-diaminopiperidines **B** or 5-amino-3-hydroxypiperidines **C**. The former have been described to act as antibacterial agents[7] or to interfere with HCV[8] or HIV[9] replication cycles, whereas the latter are central cores of some powerful JAK3 modulator **1**,[10] BTK inhibitor **2**,[11] PIM kinase modulator **3**,[12] or secretase modulator **4**.[13] As a consequence, general and versatile access to these drug-relevant scaffolds should be of great utility in a lead-oriented synthesis or for fragment-based design of novel drugs.

Among the various synthetic methods developed for the synthesis of 3,5-substituted piperidines, the ring expansion of 4-substituted prolinols developed by the group of Cossy is probably the most versatile one (Scheme 1).[6a,14] The key step

Scheme 1. Access to 3-Substituted Piperidines by Ring Expansion



of this strategy involves the opening of aziridinium intermediates leading to the formation of the six-membered **D** over the five-membered **E** rings in a ratio from 60:40 up to 100:0 depending on the regioselectivity of the ring-opening reaction.[15] According to the authors, this approach strongly relies on the bulkiness of the N and C-4 substituents, the ring expansion of *cis*-prolinols being the less selective. As a result, access to *cis* 3,5 diaminopiperidines or *cis* 5-amino-3 hydroxypiperidines can still be problematic using this strategy and lengthy alternative routes are generally chosen to prepare these scaffolds.

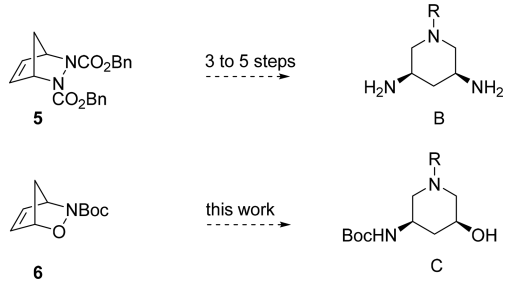
In our ongoing work on the design of RNA-binding agents,[16] we have described a general route to *cis* 3,5 diaminopiperidines of type **B** from bicyclic hydrazine **5**.[17] Herein, we wish to report that a similar approach starting from N-protected 2-oxa-3-aza

Received: June 15, 2017
Published: June 30, 2017

DOI: 10.1021/acs.joc.7b01485
J. Org. Chem. 2017, 82, 7689−7694

bicyclo[2.2.1]hept-5-ene **6** can deliver the corresponding aminoalcohols **C** in a simple and versatile manner (Scheme 2).

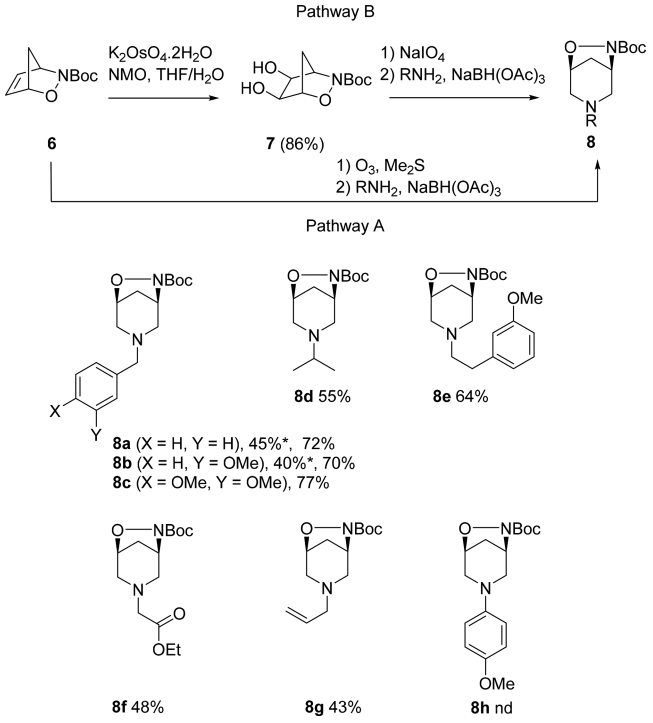
Scheme 2. Access to 3-Substituted Piperidines from Bicyclic Heterocycles



N-Boc 2-oxa-3-aza bicyclo[2.2.1]hept-5-ene **6** is a classical starting material for the synthesis of polysubstituted aminocyclopentanic compounds,[18] either in its racemic or enantioenriched form.[19] It was easily prepared on a large scale from cyclopentadiene and *tert*-butyl *N*-hydroxycarbamate in 88% isolated yield. Although many structural modifications of this classical building block have been reported for the synthesis of various compounds, most of them bearing a *cis*-1,3 aminoalcohol moiety, its homologation to the corresponding oxadiazabicyclo[3.2.1] octane via an oxidative cleavage−reductive amination sequence has surprisingly never been described.

We first investigated this route using a one-pot, two-step approach (Pathway A, Scheme 3). Ozonolysis of compound **6**, followed by reductive amination with benzylamine or 3-methoxybenzylamine led to the expected products **8a** and **8b** in respectively 45% and 40% isolated yields. In a second approach, compound **6** was first dihydroxylated in 86% yield in a fully stereoselective manner (Pathway B, Scheme 3). Oxidative cleavage of **7** followed by the reductive amination step with the same amines led to compounds **8a** and **8b** in 72% and 70% yield. Despite a two-pot procedure, this route proved to give better overall yields. Furthermore, the dihydroxylation step can be conducted on a multigram scale, leading to **7** as a storable intermediate. The scope of this route was investigated with several aliphatic or aromatic amines as well as amino ester, leading to the bicyclic adducts **8a−g** in 43 to 77% yield. Purification of compound **8h** proved to be difficult at this stage and the crude reaction mixture was used in the next step (see below).

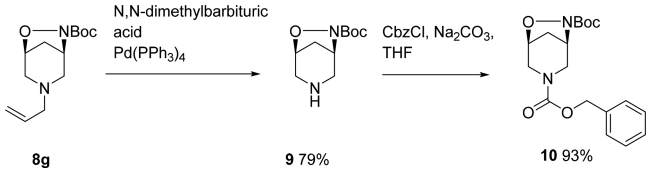
Scheme 3. Synthetic Pathways for the Preparation of Compounds 8[a]



[a]Obtained with Pathway A.

To further illustrate the flexibility of our approach, we investigated the selective deprotection of the piperidine nitrogen without cleaving the N−O bond of the bicyclic heterocycles. Thus, compound **9** could easily be obtained from compound **8g** by a palladium-catalyzed deallylation. Piperidine **9** was then submitted to a reaction with benzyl chloroformate to generate the carbamoylated product **10** in 93% yield (Scheme 4).

Scheme 4. Protective Group Interconversion



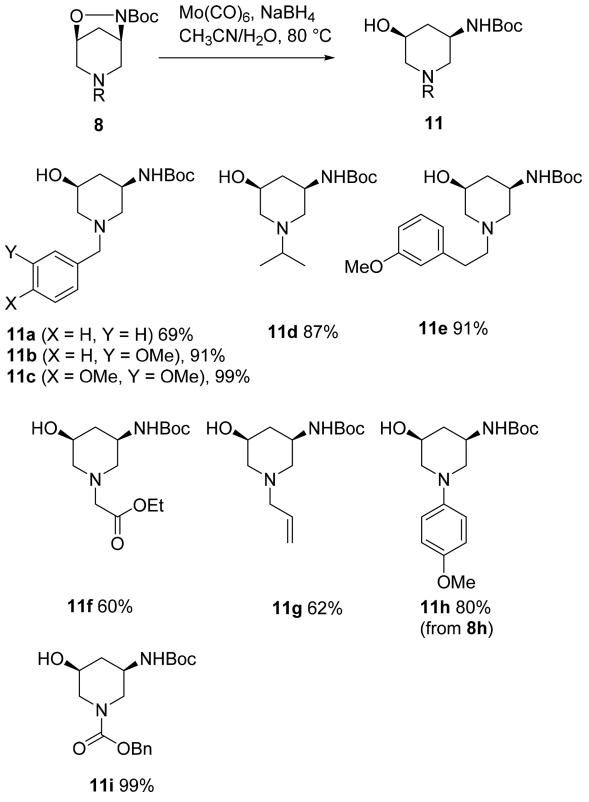
The reductive cleavage of the N−O bond was achieved using sodium borohydride in the presence of $Mo(CO)_6$ according to the procedure described by Brandi and co-workers.[20] Interestingly, the carbamate protection is unaffected by this procedure which delivers N-protected aminopiperidinols bearing various substituents on the piperidine nitrogen atom (Scheme 5). The efficiency of this synthetic route is illustrated by the preparation of compound **11f**, a PNA building block prepared in 4 steps from cyclopentadiene instead of more than 10 steps from hydroxyproline,[21] or compound **11i**, an interesting orthogonally protected building block for the design of kinases inhibitors, also prepared in 4 instead of more than 10 steps.[22]

Our strategy based on bicyclic adducts is not only limited to the preparation of *cis* 3,5 disubstituted piperidines. Compound **11i** can indeed lead to *trans* derivatives by a selective inversion of the stereogenic center bearing the hydroxyl group. This was illustrated with the preparation of compound **13** bearing 3 points of diversity available for further selective functionalization (Scheme 6).

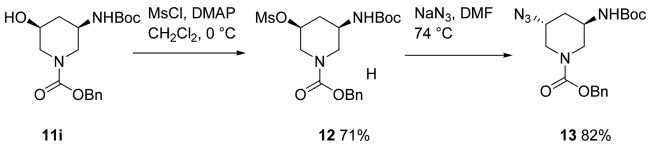
In conclusion, we have shown that 2-oxa-3-aza bicyclo[2.2.1]hept-5-ene **6**, a readily available starting material, is a suitable precursor for the preparation of N-substituted 5-amino-3-hydroxypiperidines in only 3 steps, with a broad chemical diversity and an excellent atom economy. We have also shown that a general precursor of the corresponding *trans*-3,5 diaminopiperidines is also easily obtained from the same starting material. This simple synthetic route provides a new entry to important fragments and scaffolds for the elaboration of biologically active compounds.

DOI: 10.1021/acs.joc.7b01485
J. Org. Chem. 2017, 82, 7689−7694

Scheme 5. Final Reductive Cleavage



Scheme 6. Interconversion to 3,5-*trans*-Disubstituted Piperidines



EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial suppliers and used as received without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm silica-gel (60-F254) with visualization by UV-light or staining with phosphomolybdic acid, ninhydrin, or Dragendorff's reagent. Column chromatography was performed on silica gel 60 Å (40−63 μm). All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker NMR spectrometers operating at 250 or 500 MHz (^{1}H value) and at 75 or 125 MHz (^{13}C value), respectively. HRMS spectra were recorded on a Orbitrap Mass Spectrometer or on a ESI-QToF II instrument SHIMADZU.

***tert*-Butyl 5,6-dihydroxy-2-oxa-3-azabicyclo[2.2.1]heptane-3-carboxylate 7.** To a solution of *tert*-butyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **6**[23] (3 g, 15.21 mmol) in THF (135 mL) and H_2O (13 mL) were added NMO (2.13 g, 18.25 mmol) and $K_2OsO_4{\cdot}2H_2O$ (0.04 g, 0.12 mmol). The resulting solution was stirred at r.t. for 18 h. Then the reaction was quenched by addition of a 15% $NaHSO_3$ solution. The layers were separated and the aqueous phase was washed with Et_2O (3 × 100 mL). The combined layers were dried over $MgSO_4$, filtered, and all the volatiles were removed under reduced pressure. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 99:1) afforded the desired product 7 (3.02 g, 86% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.42 (s, 9H), 1.63−1.65 (m, 1H), 2.08 (d, J = 11.5 Hz, 1H), 3.94 (s, 2H), 4.17 (bs, 1H, OH), 4.29 (s, 1H), 4.32 (bs, 1H), 4.39 (d, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.1, 31.5, 61.8, 70.0, 70.5, 79.9, 83.1, 157.2; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{10}H_{18}NO_5$ 232.1185, found 232.1175. Data in agreement with literature.[24]

Synthesis of Azabicyclo[3.2.1]octanes: Pathway A. The synthesis of *tert*-butyl 3-benzyl-6-oxa-3,7-diazabicyclo[3.2.1]octane-7-carboxylate **8a** is representative.

Ozone was bubbled into a solution of *tert*-butyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **6** (0.6 g, 3.03 mmol) in dry CH_2Cl_2 (8 mL) at −78 °C until the solution became light blue. The flask was purged with argon to remove excess ozone. The ozonide was then quenched by adding Me_2S (1.0 g, 16.22 mmol) at −78 °C. The mixture was allowed to slowly warm to room temperature and the volatiles were removed under reduced pressure to yield a yellow thick oil. CH_2Cl_2 and benzylamine (0.35 g, 3.33 mmol) were added to this mixture followed by $NaBH(OAc)_3$ (1.92 g, 9.08 mmol) and the suspension was stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (CH_2Cl_2/MeOH 99:1) afforded the desired product (0.42 g, 45% yield).

Synthesis of Azabicyclo[3.2.1]octanes: Pathway B. The synthesis of *tert*-butyl 3-benzyl-6-oxa-3,7-diazabicyclo[3.2.1]octane-7-carboxylate **8a** is representative.

To a vigorously stirred suspension of chromatographic grade silica gel (20.8 equiv) in CH_2Cl_2 (420 mL) was added dropwise a 0.65 M aqueous solution of $NaIO_4$ (7 mL, 1.4 equiv) under vigorous stirring whence a flaky suspension was formed. Diol 7 (5 g, 21.62 mmol) in CH_2Cl_2 (400 mL) was then added and the reaction was monitored by TLC until disappearance of initial product. The reaction mixture was filtered on a sintered glass packed with Na_2SO_4, concentrated, and dissolved in dry CH_2Cl_2 (10 mL), benzylamine (3.01g, 28.11 mmol) was added, followed by $NaBH(OAc)_3$ (3 equiv). The reaction was stirred 16 h at room temperature, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pleasure. Flash chromatography on silica gel (cyclohexane:ethyl acetate 80:20) afforded the desired product *tert*-butyl 3-benzyl-6-oxa-3,7-diazabicyclo[3.2.1]octane-7-carboxylate **8a**.

tert-Butyl 3-benzyl-6-oxa-3,7-diazabicyclo[3.2.1]octane-7-carboxylate ***8a***. (4.73 g, 72% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.45 (s, 9H), 1.91 (d, J = 11.0 Hz, 1H), 2.17 (d, J = 11.0 Hz, 1H), 2.19−2.23 (m, 1H), 2.26 (d, J = 11.0 Hz, 1H), 3.08 (dd, J = 11.4, 4.0 Hz, 1H), 3.25 (dd, J = 10.8, 3.5 Hz, 1H), 3.63 (AB system, $\Delta\delta$ = 0.06, J = 13.5 Hz, 2H), 4.31 (t, J = 4.5 Hz, 1H), 4.48 (t, J = 4.5 Hz, 1H), 7.26−7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.4, 37.3, 54.5, 54.7, 56.5, 61.2, 74.0, 81.4, 127.0, 128.2, 128.8, 137.4, 156.1; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{17}H_{25}N_2O_3$ 305.1865, found 305.1860.

tert-Butyl 3-(3-Methoxybenzyl)-6-oxa-3,7-diazabicyclo[3.2.1]-octane-7-carboxylate ***8b***. Synthesized according to general ozonolysis procedure. Purification by silica gel column chromatography (CH_2Cl_2/MeOH 98:2) afforded the product as yellow/brown oil, (0.34 g, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.42 (s, 9H), 1.84 (d, J = 11.0 Hz, 1H), 2.11 (d, J = 11.4 Hz, 1H), 2.12−2.16 (m, 1H), 2.19 (d, J = 10.8 Hz, 1H), 3.03 (dd, J = 11.3, 3.9 Hz, 1H), 3.17 (dd, J = 10.5, 3.5 Hz, 1H), 3.55 (AB system, $\Delta\delta$ = 0.03, J = 13.6 Hz, 2H), 3.69 (s, 3H), 4.25 (t, J = 4.5 Hz, 1H), 4.42 (t, J = 5.0 Hz, 1H), 6.69−7.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.4, 37.3, 45.5, 54.7, 55.3, 56.4, 61.1, 73.9, 81.3, 112.7, 114.2, 121.1, 129.1, 139.1, 156.0, 159.7; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{18}H_{27}N_2O_4$ 335.1971, found 335.1965.

tert-Butyl 3-(3,4-Dimethoxybenzyl)-6-oxa-3,7-diazabicyclo-[3.2.1]octane-7-carboxylate ***8c***. (0.43 g, 77% yield), as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.41 (s, 9H), 1.84 (d, J = 10.9 Hz, 1H), 2.08 (d, J = 11.4 Hz, 1H), 2.15−2.17 (m, 1H), 2.20 (d, J = 10.8 Hz, 1H), 3.01(m, 1H), 3.16 (m, 1H), 3.50 (AB system, $\Delta\delta$ = 0.09, J = 13.3 Hz, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 4.25 (bs, 1H), 4.41 (bs, 1H), 6.71−6.72 (m, 2H), 6.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.3, 37.4, 54.7, 54.8, 55.8, 55.9, 56.3, 60.8, 73.8, 81.1, 110.8, 112.0, 120.7, 130.3, 148.1, 148.9, 155.9; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{29}N_2O_5$ 365.2076, found 365.2071.

DOI: 10.1021/acs.joc.7b01485
J. Org. Chem. 2017, 82, 7689−7694

tert-Butyl 3-Isopropyl-6-oxa-3,7-diazabicyclo[3.2.1]octane-7-carboxylate ***8d***. (0.13 g, 55% yield) as yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 0.95 (dd, J = 6.3, 2.3 Hz, 6H), 1.43 (s, 9H), 1.85 (d, J = 10.0 Hz, 1H), 2.10−2.13 (m, 1H), 2.27 (bs, 2H), 2.67−2.72 (m, 1H), 2.98 (d, J = 11.5 Hz, 1H), 3.14 (d, J = 11.0 Hz, 1H), 4.30 (t, J = 4.5 Hz, 1H), 4.48 (t, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 18.0, 18.3, 28.3, 37.3, 49.9, 52.6, 53.1, 54.9, 74.2, 81.3, 156.6; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{25}N_2O_3$ 257.1865, found 257.1860.

tert-Butyl 3-(3-Methoxyphenethyl)-6-oxa-3,7-diazabicyclo[3.2.1]-octane-7-carboxylate ***8e***. (0.34 g, 64% yield), as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.50 (s, 9H), 1.89 (dd, J = 11.0, 2.0 Hz, 1H), 2.14−2.16 (m, 1H), 2.25 (dd, J = 10.5, 3.1 Hz, 2H), 2.68−2.77 (m, 4H), 3.18 (dd, J = 11.2, 3.9 Hz, 1H), 3.31 (dd, J = 9.0, 2.1 Hz, 1H), 3.77 (s, 3H), 4.42 (d, J = 4.2 Hz, 1H), 4.58 (d, J = 4.2 Hz, 1H), 6.71−6.76 (m, 3H), 7.15−7.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.3, 33.4, 37.1, 54.7, 54.9, 55.1, 56.8, 58.8, 74.2, 81.5, 111.3, 114.4, 121.0, 129.3, 141.9, 156.6, 159.7; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{29}N_2O_4$ 349.2127, found 349.2122.

tert-Butyl 3-(2-Ethoxy-2-oxoethyl)-6-oxa-3,7-diazabicyclo[3.2.1]-octane-7-carboxylate ***8f***. (0.19 g, 48% yield) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.20 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H), 1.94 (d, J = 11.1 Hz, 1H), 2.06−2.10 (m, 1H), 2.88 (d, J = 11.0 Hz, 1H), 2.92−2.97 (m, 2H), 3.04 (dd, J = 10.75, 3.0 Hz, 1H), 3.90 (AB system, $\Delta\delta$ = 0.04, J = 17.5 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 4.39 (t, J = 4.5 Hz, 1H), 4.53 (t, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 14.2, 28.3, 36.1, 53.3, 54.9, 55.0, 56.1, 60.2, 74.3, 81.6, 156.6, 170.6; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{25}N_2O_5$ 301.1763, found 301.1758.

tert-Butyl 3-Allyl-6-oxa-3,7-diazabicyclo[3.2.1]octane-7-carboxylate ***8g***. (0.14 g, 43% yield), as brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.37 (s, 9H), 1.78 (d, J = 10.9 Hz, 1H), 2.02−2.10 (m, 3H), 2.98 (bs, 3H), 3.10 (d, J = 10.5 Hz, 1H), 4.27 (bs, 1H), 4.44 (bs, 1H), 4.97−5.01 (m, 1H), 5.02−5.07 (m, 1H), 5.70−5.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.3, 37.1, 54.6, 54.9, 56.6, 60.0, 74.2, 81.5, 117.7, 134.7, 156.6; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{23}N_2O_3$ 255.1709, found 255.1703.

tert-Butyl 3-(4-Methoxyphenyl)-6-oxa-3,7-diazabicyclo[3.2.1]-octane-7-carboxylate ***8h***. (640 mg, yield not determined, isolated as 1:1 mixture with *p*-anisidine), as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.48 (s, 9H), 1.64 (bs, 1H), 2.05 (d, J = 11.1 Hz, 1H), 2.24−2.29 (m, 1H), 2.95 (ddd, J = 18.3, 11.3, 1.8 Hz, 2H), 3.75 (s, 3H), 3.77 (bs, 1H), 3.88 (ddd, J = 11.2, 3.4, 1.5 Hz, 1H), 4.64−4.67 (m, 1H), 4.77−4.79 (m, 1H), 6.63−6.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.3, 35.1, 51.3, 52.9, 54.2, 55.7, 74.0, 82.0, 113.9, 114.8, 139.9, 143.7, 156.2; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{17}H_{25}N_2O_4$ 321.1809, found 321.1811.

tert-Butyl 6-oxa-3,7-Diazabicyclo[3.2.1]octane-7-carboxylate ***9***. A solution of **8g** (300 mg, 1.18 mmol, 1 equiv) in dry CH_2Cl_2 (3.2 mL) was added to a mixture of *N*,*N*-dimethylbarbituric acid (552 mg, 3.54 mmol, 3 equiv) and tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.01 mmol, 0.01 equiv) under argon. The reaction mixture was stirred for 5 h at 35 °C in the dark, quenched with saturated aqueous $NaHCO_3$ (3 mL), and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (CH_2Cl_2/MeOH 97:3) afforded the product (0.20 g, 0.93 mmol, 79% yield) as a light yellow solid. ^{1}H NMR (500 MHz, MeOD), δ 1.49 (s, 9H), 2.04−2.07 (m, 1H), 2.20 (d, J = 11.5 Hz, 1H), 2.67 (d, J = 13.7 Hz, 1H), 2.74 (d, J = 13.4 Hz, 1H), 2.84−2.92 (m, 2H), 4.41 (dd, J = 5.6, 3.5 Hz, 1H), 4.55 (dd, J = 6.1, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, MeOD), δ 27.1, 36.2, 48.2, 49.1, 56.8, 75.5, 81.9, 156.7; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{10}H_{19}N_2O_3$ 215.1396, found 215.1390.

3-Benzyl 7-tert-butyl 6-oxa-3,7-Diazabicyclo[3.2.1]octane-3,7-dicarboxylate ***10***. A solution of compound **9** (79 mg, 0.37 mmol) in a mixture of THF (5 mL) and 1 M aq. soln. Na_2CO_3 (5 mL) was prepared and stirred for 5 min. CbzCl (252 mg, 1.47 mmol) was slowly added and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/Cyclohexane 80:20) afforded the product (0.079 g, 0.34 mmol, 93% yield) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.41 (s, 9H), 1.92 (d, J = 11.4 Hz, 1H), 2.07−2.12 (m, 1H), 2.98−3.02 (m, 1H), 3.05−3.10 (m, 1H), 3.98 (d, J = 13.5 Hz, 1H), 4.03−4.10 (m, 1H), 4.47 (d, J = 26.2 Hz, 1H), 4.59 (d, J = 34.8 Hz, 1H), 5.05 (AB system, $\Delta\delta$ = 0.03, J = 13.6 Hz, 2H),7.19−7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.2, 34.5, 48.4, 49.6, 53.4, 67.3, 73.1, 82.3, 127.9, 128.0, 128.5, 136.5, 155.6, 156.1; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{18}H_{25}N_2O_5$ 349.1763, found 349.1758.

General Procedure for Reductive Cleavage. The synthesis of *tert*-butyl (1-benzyl-5-hydroxypiperidin-3-yl)carbamate **11a** is representative.

In a 25 mL single-necked round-bottomed flask azabicyclo[3.2.1]-octanes **8a** (170 mg, 0.508 mmol) was dissolved in 8 mL of a 4:1 CH_3CN/H_2O mixture at 50 °C. Then $Mo(CO)_6$ (81 mg, 0.305 mmol) was added to the solution in one portion, followed by $NaBH_4$ (64 mg, 1.678 mmol) added in small portions. Bubbling was observed and the color of the reaction changed from light yellow to a deep, murky brown. After the bubbling subsided, the reaction was heated to 80 °C and the mixture was stirred overnight. Finally, the reaction mixture was filtered through a pad of Celite and concentrated. The crude product was dissolved in ethyl acetate (10 mL), a saturated solution of $NaHCO_3$ (10 mL) was added and the mixture was stirred overnight. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography by silica gel (CH_2Cl_2/MeOH 98:2) afforded the desired product.

tert-Butyl ((3S,5R)-1-Benzyl-5-hydroxypiperidin-3-yl)carbamate ***11a***. (0.35 g, 69% yield), as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6), δ 1.08 (ddd, J = 23.0, 11.5, 11.5, Hz, 1H), 1.37 (s, 9H), 1.64 (dd, J = 22.2, 9.9 Hz, 2H), 1.92 (m, 1H), 2.78 (bs, 2H), 3.34−3.56 (m, 4H), 4.72 (bs, 1H), 6.77 (d, J = 8.3 Hz, 1H), 7.23−7.34 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6), δ 28.2, 39.9, 45.9, 57.9, 59.9, 61.5, 65.1, 77.6, 126.9, 128.1, 128.7, 138.2, 154.8; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{17}H_{27}N_2O_3$ 307.2022, found 307.2016.

tert-Butyl (5-Hydroxy-1-(3-methoxybenzyl)piperidin-3-yl)-carbamate ***11b***. (0.16 g, 91% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.33 (s, 9H), 1.38 (bs, 1H), 1.85 (bs, 1H), 2.14−2.16 (m, 1H), 2.26 (bs, 2H), 2.49 (bs, 2H), 2.66 (bs, 1H), 3.42 (AB system, $\Delta\delta$ = 0.03, J = 13.5 Hz, 2H), 3.71 (s, 3H), 3.80 (bs, 1H), 5.2 (bs, 1H), 6.69−6.71 (m, 1H), 6.78−6.80 (m, 2H), 7.11−7.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.4, 37.3, 45.7, 55.2, 57.9, 59.5, 62.3, 66.1, 79.2, 112.7, 114.4, 121.3, 129.3, 139.3, 155.3, 159.6; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{18}H_{29}N_2O_4$ 337.2127, found 337.2133.

tert-Butyl (1-(3,4-Dimethoxybenzyl)-5-hydroxypiperidin-3-yl)-carbamate ***11c***. (0.13 g, 99% yield) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.34 (s, 9H), 1.43 (bs, 1H), 1.84 (bs, 1H), 2.30 (bs, 3H), 2.48 (bs, 2H), 3.40 (AB system, $\Delta\delta$ = 0.03, J = 13.5 Hz, 2H), 3.69 (bs, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 3.81−3.83 (m, 1H), 5.15 (bs, 1H), 6.72 (s, 2H), 6.80 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.4, 37.3, 45.7, 55.9, 57.9, 59.5, 62.0, 66.2, 77.4, 79.2, 110.9, 112.0, 121.1, 130.4, 148.2, 148.9, 155.2; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{31}N_2O_5$ 367.2233, found 367.2227.

tert-Butyl (5-Hydroxy-1-isopropylpiperidin-3-yl)carbamate ***11d***. (0.11 g, 87% yield), as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6), δ 0.92−1.02 (m, 6H), 1.06 (ddd, J = 22.7, 11.5, 11.0 Hz, 1H), 1.37 (s, 9H), 1.79 (bs, 2H), 1.91 (bs, 1H), 2.50−2.52 (m, 3H), 3.35 (bs, 1H), 3.45 (bs, 1H), 4.70 (bs, 1H), 6.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6), δ 17.4, 17.9, 28.2, 39.7, 46.2, 53.5, 54.8, 55.4, 65.5, 77.5, 154.8; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{27}N_2O_3$ 259.2022, found 259.2016.

tert-Butyl (5-Hydroxy-1-(3-methoxyphenethyl)piperidin-3-yl)-carbamate ***11e***. (0.11 g, 87% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.36 (s, 9H), 1.43 (bs, 1H), 1.83 (bs, 1H), 2.34 (bs, 2H), 2.45−2.57 (m, 4H), 2.65−2.68 (m, 2H), 2.82 (m, 1H), 3.71 (s, 4H), 3.81 (bs, 1H), 5.20 (bs, 1H), 6.64−6.70 (m, 3H), 7.09−7.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 27.5, 32.2, 36.1, 44.7, 54.1, 56.8, 58.6, 59.0, 65.0, 78.2, 110.4, 113.4, 120.1, 128.3, 140.8, 154.3,

DOI: 10.1021/acs.joc.7b01485
J. Org. Chem. 2017, 82, 7689−7694

158.6; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{31}N_2O_4$ 351.2284, found 351.2278.

Ethyl 2-(3-((tert-Butoxycarbonyl)amino)-5-hydroxypiperidin-1-yl)acetate **11f**. (0.04 g, 60% yield), as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6), δ 0.95−1.02 (m, 1H), 1.13 (t, J = 7.1, 3H), 1.32 (s, 9H), 1.78−1.92 (m, 3H), 2.70 (dd, J = 10.5, 4.3 Hz, 1H), 2.76 (dd, J = 10.4, 4.5 Hz, 1H), 3.20 (d, J = 5.7 Hz, 2H), 3.37−3.44 (m, 2H), 4.02 (q, J = 7.1 Hz, 2H), 4.69 (d, J = 4.9 Hz, OH), 6.72 (d, J = 8.1 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6), δ 14.1, 28.2, 39.7, 45.8, 56.8, 57.9, 59.2, 65.0, 77.5, 81.7, 154.8, 170.0; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{27}N_2O_5$ 303.1920, found 303.1900.

tert-Butyl (1-Allyl-5-hydroxypiperidin-3-yl)carbamate **11g**. (0.03 g, 62% yield) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.37 (s, 9H), 1.43−1.49 (m, 1H), 1.85 (bs, 1H), 2.28−2.48 (m, 5H), 2.96 (dd, J = 6.6, 1.3 Hz, 2H), 3.70 (bs, 1H), 3.85 (bs, 1H), 5.07−5.13 (m, 2H), 5.17 (bs, 1H), 5.76 (ddd, J = 16.7, 10.1, 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 27.4, 35.9, 44.5, 56.8, 58.6, 60.1, 65.0, 78.2, 117.2, 133.5, 154.2; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{25}N_2O_3$ 257.1865, found 257.1860.

tert-Butyl (5-Hydroxy-1-(4-methoxyphenyl)piperidin-3-yl)carbamate **11h**. (0.12 g, 80% yield) as a white powder. ^{1}H NMR (500 MHz, MeOD), δ 1.20 (dd, J = 22.5, 11.0 Hz, 1H), 1.34 (s, 9H), 2.05−2.08 (m, 1H), 2.29 (t, J = 10.6 Hz, 1H), 2.35 (t, J = 10.3 Hz, 1H), 3.35−3.37 (m, 2H), 3.62 (bs, 1H), 3.62 (s, 3H), 3.68−3.73 (m, 1H), 6.70−6.72 (m, 2H), 6.81−6.83 (m, 2H); ^{13}C NMR (125 MHz, MeOD), δ 28.8, 40.1, 47.4, 55.9, 57.4, 59.2, 66.9, 80.2, 115.5, 120.4, 146.6, 155.7, 157.8; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{17}H_{27}N_2O_4$ 323.1971, found 323.1965.

Benzyl 3-((tert-Butoxycarbonyl)amino)-5-hydroxypiperidine-1-carboxylate **11i**. (0.115 g, 99% yield) as a light yellow solid. ^{1}H NMR (500 MHz, MeOD), δ 1.41 (s, 10H), 2.09 (d, J = 12.8 Hz, 1H), 2.98 (bs, 2H), 3.53 (bs, 1H), 3.68 (bs, 1H), 3.84 (bs, 1H), 5.12 (s, 2H), 7.28−7.37 (m, 5H); ^{13}C NMR (125 MHz, MeOD), δ 27.3, 35.4, 37.3, 45.4, 49.6, 64.6, 67.0, 78.9, 127.4, 127.6, 128.1, 136.6, 155.8, 156.6; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{18}H_{27}N_2O_5$ 351.1920, found 351.1914.

Benzyl 3-((tert-Butoxycarbonyl)amino)-5-((methylsulfonyl)oxy)-piperidine-1-carboxylate **12**. Hydroxypiperidine **11i** (0.115 g, 0.33 mmol) and DMAP (0.281 g, 2.29 mmol) were coevaporated with anhydrous dichloromethane (DCM) and suspended in 6 mL DCM. The mixture was cooled to 0 °C and mesyl chloride (0.263 g, 2.29 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h. Water (2 mL) was added and stirring continued for an additional 10 min. DCM (10 mL) was added to the mixture and the organic phase was washed with saturated solution of $NaHCO_3$. The organic phases were dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated. The crude mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc 70:30). The product **12** was obtained as a white amorphous solid (0.101 g, 71% yield). ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C), δ 1.39 (s, 9H), 1.53−1.60 (m, 1H), 2.23−2.26 (m, 1H), 3.25 (s, 3H), 3.31 (bs, 1H), 3.50 (bs, 1H), 3.89 (bs, 1H), 3.98 (bs, 1H), 4.23 (dd, J = 12.5, 4.8 Hz, 1H), 4.59−4.64 (m, 1H), 5.10 (d, J = 16.5 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H), 7.31−7.40 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C), δ 28.1, 36.1, 37.3, 45.2, 47.2, 50.0, 66.5, 73.5, 78.1, 127.3, 127.8, 128.4, 136.6, 154.1, 154.8; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{29}N_2O_7S$ 429.1695, found 429.1690.

Benzyl 3-Azido-5((tert-butoxycarbonyl)amino)piperidine-1-carboxylate **13**. To a solution of compound **12** (50 mg, 0.12 mmol), in dry DCM (63 equiv), was added in small portions NaN_3 (30 mg, 0.46 mmol) at rt. The mixture was heated to 77 °C for 16 h. After allowing the mixture to cool to rt, sat. aq. $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified through a silica gel flash column (cyclohexane/EtOAc 100:0 to 80:20) to afford desired compound (0.036 g, 82% yield) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C), δ 1.40 (s, 9H), 1.74 (ddd, J = 13.5, 9.7, 3.6 Hz, 1H), 1.87−1.92 (m, 1H), 2.96 (bs, 1H), 3.28 (dd, J = 13.8, 2.9 Hz, 1H), 3.56−3.62 (m, 1H), 3.73 (d, J = 14.0 Hz, 1H), 3.84 (dd, J = 12.1, 3.9 Hz, 1H), 4.03 (ddd, J = 8.3, 4.9, 3.2 Hz, 1H), 5.11 (s, 2H), 6.60 (bs, 1H), 7.29−7.43 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C), δ 28.7, 34.4, 43.8, 46.9, 48.2, 55.7, 66.9, 78.6, 127.8, 128.2, 128.7, 137.4, 151.3, 155.3; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{18}H_{26}N_5O_4$ 376.1985, found 376.1979.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01485.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*laurent.micouin@parisdescartes.fr

ORCID

Laurent Micouin: 0000-0003-1080-8591

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully thank the Université Paris Descartes, CNRS, and CONACYT (grant to P.G. No. 263905) for financial support.

■ REFERENCES

(1) Papp, K. A.; Krueger, J. G.; Feldman, S. R.; Langley, R. G.; Thaci, D.; Torii, H.; Tyring, S.; Wolk, R.; Gardner, A.; Mebus, C.; Tan, H.; Luo, Y.; Gupta, P.; Mallbris, L.; Tatulych, S. *J. Am. Acad. Dermatol.* **2016**, *74*, 841−850.

(2) Kim, E. S.; Dhillon, S. *Drugs* **2015**, *75*, 769−776.

(3) Christopher, R.; Covington, P.; Davenport, M.; Fleck, P.; Mekki, Q. A.; Wann, E. R.; Karim, A. *Clin. Ther.* **2008**, *30*, 513−527.

(4) Forst, T.; Pfützner, A. *Expert Opin. Pharmacother.* **2012**, *13*, 101−110.

(5) Yang, L. P. H.; Scott, L. J. *Drugs* **2009**, *69*, 2257−2278.

(6) (a) Gomez Pardo, D.; Cossy, J. *Chem. - Eur. J.* **2014**, *20*, 4516−4525. and references cited. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845−5859.

(7) (a) Zhou, Y.; Gregor, V. E.; Sun, Z.; Ayida, B. K.; Winters, G. C.; Murphy, D.; Simonsen, K. B.; Vourloumis, D.; Fish, S.; Froelich, J. M.; Wall, D.; Hermann, T. *Antimicrob. Agents Chemother.* **2005**, *49*, 4942−4949. (b) Zhou, Y.; Chow, C.; Murphy, D. E.; Sun, Z.; Bertolini, T.; Froelich, J. M.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3369−3375.

(8) Carnevali, M.; Parsons, J.; Wyles, D. L.; Hermann, T. *ChemBioChem* **2010**, *11*, 1364−1367.

(9) Micouin, L.; Blond, A.; Calvez, V.; Marcellin, A.-G.; Soulié, C.; Corrot, E. Patent WO2015181387A1, December 3, 2015.

(10) Brown, M. F.; Casimoro-Garcia, A.; Che, Y.; Coe, J. W.; Flanagan, M. E.; Gilbert, A/ M.; Hayward, M. M.; Langille, J. D.; Montgomery, J. I.; Telliez, J.-B.; Thorarensen, A.; Unwalla, R. J. Patent WO2015083028A1, June 11, 2015.

(11) Erlanson, D.; Marcotte, D.; Kumaravel, G.; Fan, J.; Wang, D.; Cuervo, J.; Silvian, L., Powell, N.; Bui, M.; Hopkins, B. T.; Taveras, A.; Guan, B.; Conlon, P.; Zhong, M.; Jenkins, T.; Scott, D.; Lugovskoy, A. A. Patent WO2011029046A1, May 10, 2011.

(12) Burger, M.; Jiong, L. Patent WO201026122A1.

(13) (a) Pettersson, M.; Stepan, A. F.; Kauffman, G.; Johnson, D. S. *Expert Opin. Ther. Pat.* **2013**, *23*, 1349−1366. (b) Iwama, S.; Kato, Y.; Kobayashi, T.; Fusano, A. Patent WO2011059048A1, May 19, 2011.

(14) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442−4445.

(15) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2012**, *2012*, 2023−2040.

(16) (a) Chung, F.; Tisné, C.; Lecourt, T.; Dardel, F.; Micouin, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 4489−4491. (b) Chung, F.; Tisné, C.; Lecourt, T.; Seijo, B.; Dardel, F.; Micouin, L. *Chem. - Eur. J.* **2009**, *15*, 7109−7116. (c) Moumné, R.; Larue, V.; Seijo, B.; Lecourt, T.;

DOI: 10.1021/acs.joc.7b01485
J. Org. Chem. 2017, 82, 7689−7694

Micouin, L.; Tisné, C. *Org. Biomol. Chem.* **2010**, *8*, 1154−1159. (d) Moumné, R.; Catala, M.; Larue, V.; Micouin, L.; Tisné, C. *Biochimie* **2012**, *94*, 1607−1619. (e) Guyon, H.; Mavré, F.; Catala, M.; Turcaud, S.; Brachet, F.; Limoges, B.; Tisné, C.; Micouin, L. *Chem. Commun.* **2017**, *53*, 1140−1143.
(17) Blond, A.; Dockerty, P.; Álvarez, R.; Turcaud, S.; Lecourt, T.; Micouin, L. *J. Org. Chem.* **2013**, *78*, 12236−12242.
(18) (a) Memeo, M. G.; Quadrelli, P. *Chem. Rev.* **2017**, *117*, 2108−2200. (b) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630−5647.
(19) (a) Brulikova, L.; Harrison, A.; Miller, M. J.; Hlavac, J. *Beilstein J. Org. Chem.* **2016**, *12*, 1949−1980. (b) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885−888.
(20) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3355.
(21) Kovačková, A.; Dračínský, M.; Rejman, D. *Tetrahedron* **2011**, *67*, 1485−1500.
(22) Zhou, Y.; Voulourmis, D.; Gregor, V. E.; Winters, G.; Hermann, T.; Ayida, B.; Sun, Z.; Murphy, D.; Simonsen, K. B. Patent WO2005028467A1, March 31, 2005.
(23) Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M.-C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. *Tetrahedron* **2004**, *60*, 2559−2567.
(24) Cowart, M.; Bennett, M. J.; Kerwin, J. F., Jr. *J. Org. Chem.* **1999**, *64*, 2240−2249.

DOI: 10.1021/acs.joc.7b01485
J. Org. Chem. 2017, 82, 7689−7694