OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Strategic Approach to the Metamorphosis of γ-Lactones to NH γ-Lactams via Reductive Cleavage and C−H Amidation

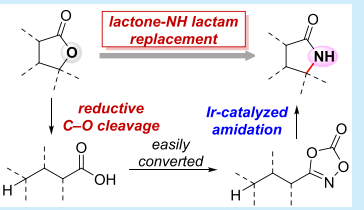
Hoi-Yun Jung,[†,‡] Sukbok Chang,[*,‡,†] and Sungwoo Hong[*,‡,†]

[†]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea

[‡]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Korea

Supporting Information

ABSTRACT: A new approach has elaborated on the conversion of γ-lactones to the corresponding NH γ-lactams that can serve as γ-lactone bioisosteres. This approach consists of reductive C−O cleavage and an Ir-catalyzed C−H amidation, offering a powerful synthetic tool for accessing a wide range of valuable NH γ-lactam building blocks starting from γ-lactones. The synthetic utility was further demonstrated by the late-stage transformation of complex bioactive molecules and the asymmetric transformation.



The lactone moiety is a common structural motif present in a variety of biologically active natural products and pharmaceuticals.[1] However, due to the metabolic instability of lactone rings in various bioactive molecules, their cellular and in vivo activities are often significantly reduced.[2] The NH-free γ-lactam building block has long been recognized as a privileged scaffold in medicinal chemistry and can be considered a bioisostere[3] of the γ-lactone moiety. Indeed, the effectiveness of the lactone-to-lactam replacement has been well validated in drug discovery.[4] For example, *dl*-3-*N*-butylphthalide (*dl*-NBP, **1a**), isolated from the seed of *Apium graveolens Linn,* is a γ-lactone-containing drug for the treatment of ischemic strokes (Figure 1).[4c,d] However, the low

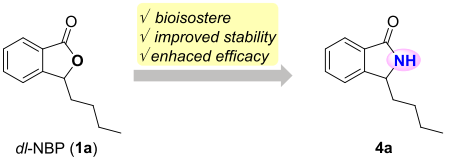


Figure 1. Example of a lactone drug to an NH lactam.

efficacy of *dl*-NBP has been attributed to its poor aqueous solubility and metabolic instability.[4c,d] On the other hand, the NH γ-lactam derivative **4a** was successfully identified as a bioisostere, which exhibited remarkably improved oral bioavailability and *in vivo* antiplatelet aggregation activity.[4]

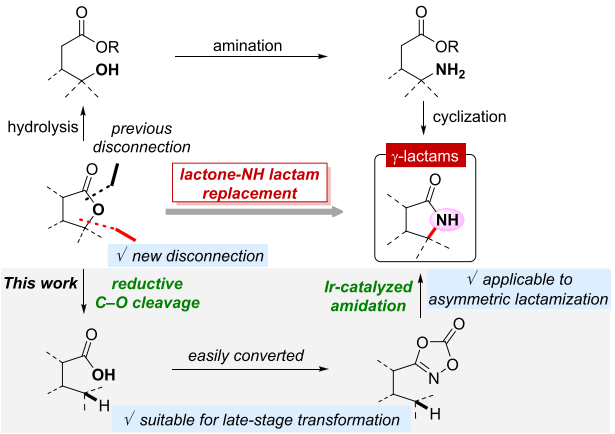
With this advantage, the γ-lactone/γ-lactam replacement presents an attractive strategy for directly accessing NH-free γ-lactam privileged structures that could improve the physicochemical properties while maintaining or even enhancing the bioactivity through the formation of new hydrogen bonds between the lactam NH and the active site of biological targets.[5] Besides, newly synthesized γ-lactam scaffolds are of high interest for the exploration of chemical space by rapidly accessing structural diversity, which might have never been evaluated otherwise. As a result, the lactone-to-NH lactam conversion has been studied extensively. The effective general methods for carrying out the synthesis of the NH-free lactams from lactones mostly involve three sequential steps that consist of ring opening of lactone, amination, and intramolecular cyclization.[6] Despite these advances reported in the field thus far, current methods are often problematic in applications mainly due to the harsh reaction conditions and/or high ammonia pressures,[6a] which limit their utility to the transformation of simple lactone substrates, which are unstable under hydrolysis conditions. Moreover, the asymmetric version of lactone-to-lactam conversion has thus far remained out of reach. With the need for increasing the structural complexity in medicines, there is a growing demand for new approaches to the lactone-to-NH lactam conversion to streamline drug discovery research.

As outlined in Scheme 1, we envisioned that a new retrosynthetic analysis using the power of a C−H functionalization disconnection approach would enable efficient, direct, and even enantioselective construction of challenging NH γ-lactams starting from γ-lactones. Previously, we reported a straightforward method for preparing γ-lactams by the intramolecular insertion of Ir-nitrenoids into C−H bonds by employing 1,4,2-dioxazol-5-ones as useful amidating agents.[7d,g] Drawing inspiration from these studies, we speculated that a synthetically useful lactone-to-NH lactam conversion could be developed via the combination of reductive C−O cleavage of the lactone and subsequent direct C−H amidation.[7] If successful, such a powerful synthetic strategy would represent a convenient platform to convert γ-lactone to NH γ-lactam scaffold in a predictable and controllable manner. Under the optimized reaction conditions, we discovered that a wide range of NH γ-lactams could be formed with high efficiency. The convenience of this protocol was illustrated by converting an important class of complex natural products and bioactive

Received: July 30, 2019

DOI: 10.1021/acs.orglett.9b02673
Org. Lett. XXXX, XXX, XXX−XXX

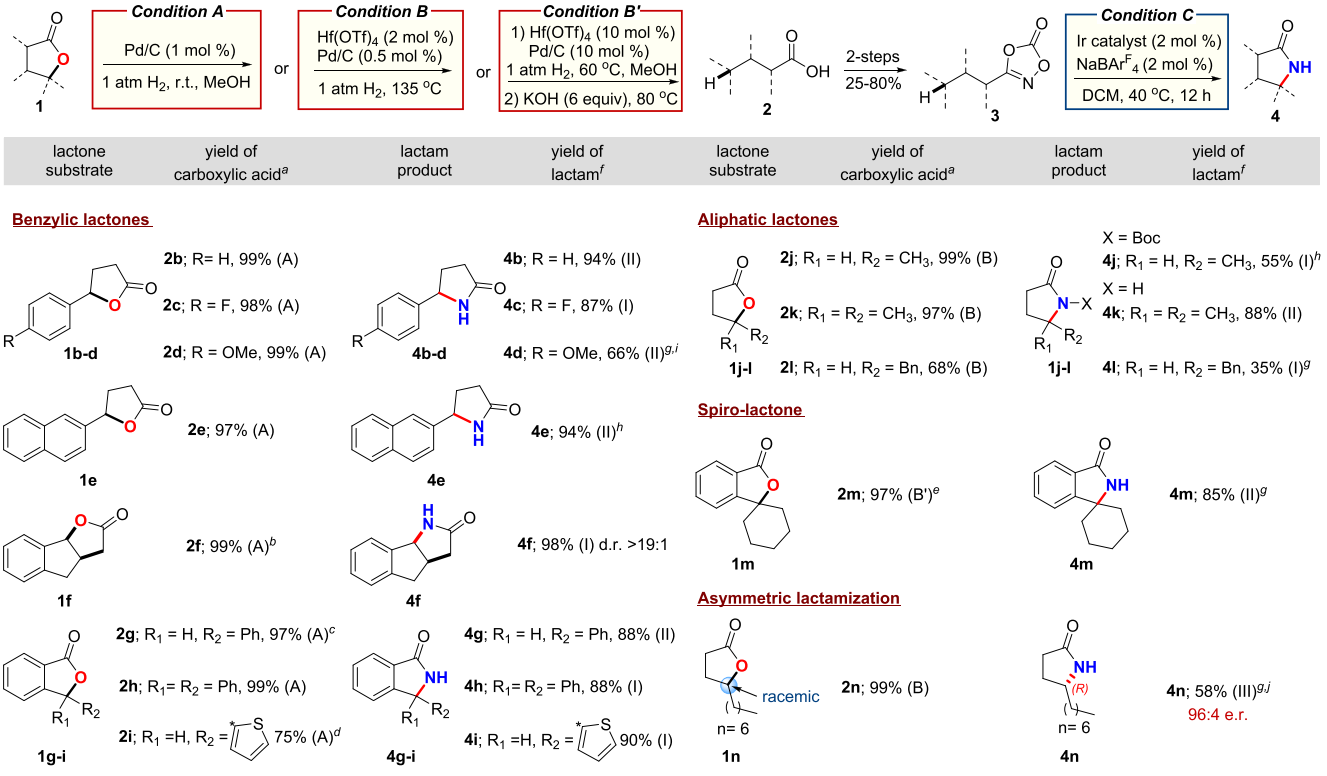
Scheme 1. Approaches to NH-Free γ-Lactam Synthesis from γ-Lactones



molecules containing γ-lactone cores into the corresponding valuable NH γ-lactam analogues. Moreover, the utility of this powerful transformation was further demonstrated in the successful asymmetric formation from a racemic γ-lactone.

Based on the above considerations, we explored the feasibility of our proposed ideas by initially testing the Pd-catalyzed reductive cleavage of the C−O bond of various simple substrates containing γ-lactones, as shown in Table 1. The benzylic lactones could readily undergo catalytic hydrogenolysis to afford the corresponding carboxylic acids in excellent yield.[8a,b] Substrates bearing aryl motifs, as exemplified by phenyl (**1b**), *p*-fluorophenyl (**1c**), *p*-methoxyphenyl (PMP) (**1d**), and naphthyl groups (**1e**), readily participated in the reaction and provided the desired products (**2b−e**). Tricyclic lactone **1f**, easily found in the synthetic phytohormone strigolactone,[9] reacted well to afford the corresponding carboxylic acid **2f** in excellent yield. Further exploration demonstrated that a series of phthalides containing (hetero)-arenes, such as phenyl (**1g**), diphenyl (**1h**), and thiophene-yl (**1i**) could be successfully subjected to these reaction conditions and generated the corresponding carboxylic acids. In sharp contrast, it was observed to be difficult to selectively cleave the C_{alkoxy}−O bond in nonbenzylic lactones by conventional Pd-catalyzed hydrogenolysis. Because a Lewis acid can promote C_{alkoxy}−O bond activation with olefins,[8c,d] we wondered whether it could invoke the catalytic hydrogenation reactivity by exploiting the effect of a series of Lewis acids. To our delight, the reductive ring-opening of nonbenzylic lactones was successfully achieved by adding a catalytic amount of metal triflates, where $Hf(OTf)_4$ was found to be most efficient in this reaction, and the desired products were readily obtained[8d] (see the Supporting Information for details). After systematic variation of different reaction parameters, the optimal conditions were identified and then applied to a variety of nonbenzylic lactones to investigate the scope of the reaction. The lactone substrates bearing various alkyl substituents, including methyl (**1j**), dimethyl (**1k**), benzyl (**1l**), and heptyl

Table 1. Scope of the Lactone-to-NH Lactam Conversion



[a]Conditions A: 1 mol % Pd/C and **1** (2 mmol) in MeOH at rt under 1 atm H_2 for 1−12 h. Conditions B: 0.5 mol % Pd/C, 2 mol % $Hf(OTf)_4$, and **1** (2 mmol) without solvent at 135 °C under 1 atm H_2 for 12 h. Conditions B′: 10 mol % Pd/C, and 10 mol % $Hf(OTf)_4$ and **1** (1 mmol) in MeOH (1 mL) at 60 °C under 1 atm H_2 for 12 h. [b]10 mol % Pd/C. [c]5 mol % Pd/C. [d]10 mol % Pd/C in AcOH at 90 °C for 4 h. [e]*n*BuOH at 120 °C. [f]Conditions C: **3** (0.1 mmol), Ir catalyst (2 mol %), and $NaBAr^F_4$ (2 mol %) in CH_2Cl_2 (1.2 mL) at 35−50 °C. [g]10 mol % Ir catalyst. [h]5 mol % Ir catalyst. [i]80 °C for 48 h. [j]Tetrachloroethane at 35 °C for 24 h.

DOI: 10.1021/acs.orglett.9b02673
Org. Lett. XXXX, XXX, XXX−XXX

(**1n**) groups, proceeded well under conditions B to afford the desired products (**2j–l** and **2n**) in modest to good yields. In addition, expanding the scope to a spiro-lactone **1m** was also feasible in an alcoholic solvent, giving rise to ester, and subsequent hydrolysis produced the corresponding carboxylic acid **2m**.

With various 1,4,2-dioxazol-5-ones accessed from carboxylic acids and esters,[7d] we next examined the reaction scope of the intramolecular C–H amidation catalyzed by the Ir catalysts displayed in Figure 2. Dioxazolones containing benzylic C–H

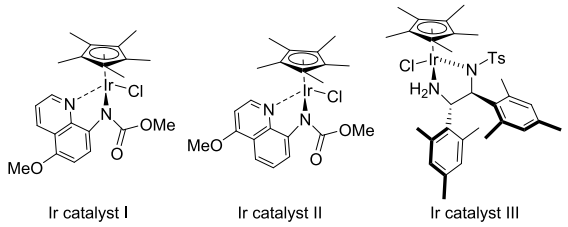


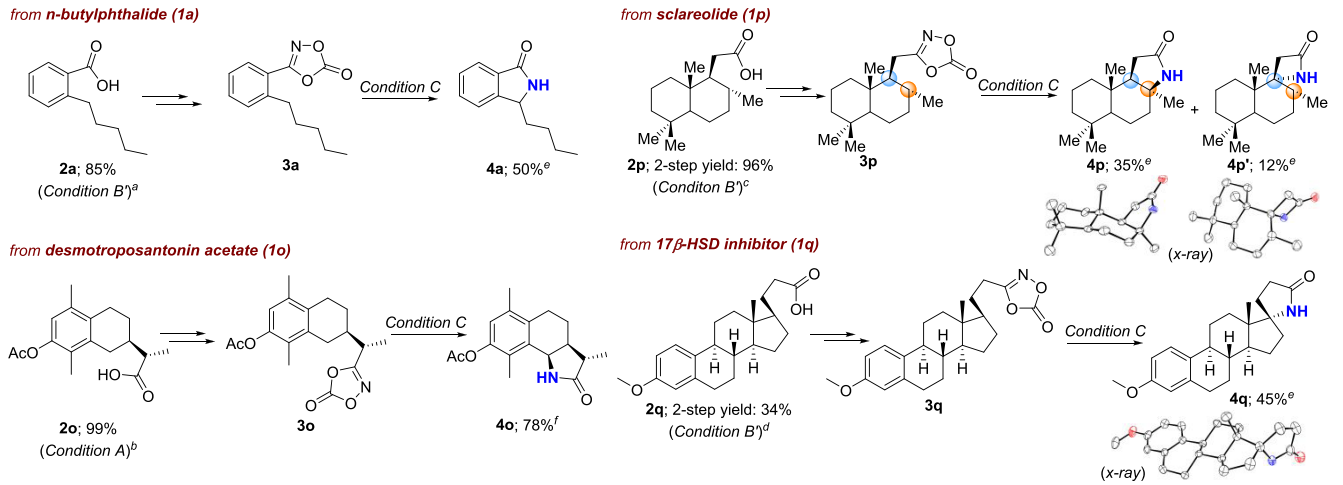
Figure 2. Ir catalysts used for the intramolecular C–H amidation.

bonds were readily converted to the corresponding γ-lactams in high yields. The cyclization of substrates bearing phenyl, 4-fluorophenyl, PMP, and naphthyl groups provided γ-lactams (**4b–e**) in moderate to high yields. A tricyclic γ-lactam (**4f**), which is a building block of strigolactam,[10] could be constructed from a secondary benzylic C–H bond in the indane ring. A series of dioxazolones prepared from phthalides containing (hetero)arenes, such as phenyl, diphenyl, and thiophene, could be successfully subjected to these reaction conditions to generate the corresponding isoindolines (**4g–i**). The optimal conditions were then applied to a variety of nonbenzylic lactones to investigate the scope of the reaction. The amidation of nonactivated secondary C–H bonds of methyl, dimethyl, and benzyl groups was successful and resulted in the corresponding products (**4j–l**). The tertiary C–H bond in the cyclohexyl group reacted well under conditions C to afford spiro-lactam **4m**. Motivated by these findings, we next investigated the lactone-to-NH lactam conversion in an asymmetric version and successfully achieved enantioselective lactamization (**4n**) at an aliphatic secondary C–H bond adjacent to the heptyl position with >96:4 er by employing Ir catalyst **III** bearing a chiral hydrogen-bond donor ligand.[7g]

To further test the generality of this approach, the synthetic applicability to medicinally relevant molecules and polycyclic natural products was also investigated as summarized in Scheme 2. A natural product, *dl*-NBP (**1a**) was initially subjected to conditions B′ using methanol as the solvent; however, the reactivity turned out to be poor. Remarkably, the use of ethyl acetate as the solvent notably enhanced the C–O bond cleavage reaction, and we were successfully able to obtain the carboxylic acid (**2a**), which was readily converted to the dioxazolone. Subsequently, Ir catalyst **I** was employed to transform the dioxazolone (**3a**) to the desired lactam **4a**. Next, we turned to desmotoroposantonin acetate, a sesquiterpene lactone derivative that is known to have immunosuppressive effects,[11] and the corresponding carboxylic acid (**2o**) was obtained in excellent yield via the established hydrogenolysis procedure. The subsequent C–H amidation of the dioxazolone derivative resulted in 78% yield of the lactam product **4o**. (*R*)-(+)-Sclareolide is another sesquiterpene lactone that has been extracted from various plants,[12] which has been used as a starting material for the synthesis of bioactive derivatives, especially as an antifungal agent.[12] Exposing this natural product to conditions B′, we obtained the methyl ester, and subsequent hydrolysis gave the carboxylic acid (**2p**) in 96% two-step yield. During the Lewis acid promoted lactone cleavage, the stereochemistry of the tertiary carbon was inverted, where the methyl group is in the equatorial position, as confirmed by NOESY NMR studies (see the SI for details). In the subsequent intramolecular C–H amidation reaction of dioxazolone **3p**, two adjacent tertiary C–H bonds were found to react to produce 4-membered and 5-membered lactams: γ-lactam **4p** and spiro-β-lactam **4p′** were confirmed by nuclear magnetic resonance (NMR) and X-ray diffraction (XRD) analysis.

This strategy was then applied to develop a novel γ-lactam-containing inhibitor accessible from a bioactive γ-lactone scaffold. After screening chemical libraries in our group, spiro-lactone **1q** was identified as a new hit against bromodomain (BRD) 2-1 to regulate uncontrolled gene transcription.[13] To

Scheme 2. Late-Stage Transformation of γ-Lactones into the NH γ-Lactams



[a]Run in dry ethyl acetate at 70 °C. [b]5 mol % Pd/C was used. [c]Run in AcOH at 60 °C (97% yield). [d]20 mol % $Hf(OTf)_4$ was used. [e]10 mol % Ir catalyst was used. [f]5 mol % Ir catalyst was used.

DOI: 10.1021/acs.orglett.9b02673
Org. Lett. XXXX, XXX, XXX–XXX

the best of our knowledge, BRD inhibitors bearing a steroid scaffold have not yet been reported. To identify more potent BRD inhibitors, we investigated the binding mode of a newly identified inhibitor, spiro-lactone **1q**, in the active site of BRD 2-1 employing the crystal structure (PDB 2DVQ) as a template.[14] Interestingly, our docking studies revealed that the NH lactam ring could confer favorable binding forces by serving as a hydrogen-bond donor with the carboxylate side chain of ASP160 as presented in Figure 3. Based on this

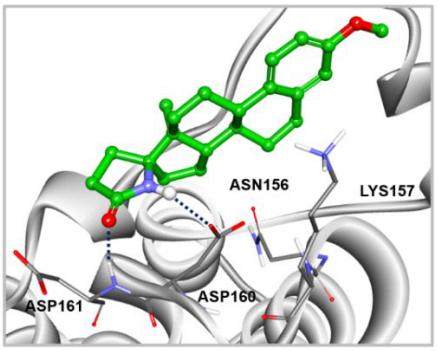
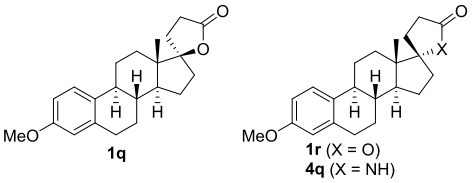


Figure 3. Calculated binding mode of **4q** at the active site of BRD 2-1 (PDB 2DVQ). Each dotted line indicates a hydrogen bond.

structural analysis, we wondered whether the lactone-to-NH lactam conversion might improve the potency by establishing an additional H-bond. Using the developed synthetic strategy, NH γ-lactam compound **4q** was successfully obtained starting from **1q**, and its structure was confirmed by the X-ray crystallographic analysis (Scheme 2). The inverted spiro-lactone **1r** was also prepared[15] as a control compound. Intriguingly, newly synthesized NH lactam **4q** showed improved inhibitory activity against BRD 2-1 (IC_{50} value of 79 μM)[16] when compared to those of the original lactone **1q** and **1r**, as enumerated in Table 2. This result illustrates that the novel scaffold **4q** has the potential to be a good starting point from which more potent BRD inhibitors can be derived.

Table 2. BRD 2-1 Inhibition Activity



compd	inhibition (%) at 50 μM	inhibition (%) at 100 μM	IC_{50} (μM)
1q		34	>100
1r		33	>100
4q	36	60	79

In conclusion, we have developed a convenient synthetic approach to the lactone-to-NH lactam conversion that features the combination of reductive C−O cleavage of the lactone and subsequent direct C−H amidation. This powerful strategy allows accessing a wide range of valuable NH γ-lactam building blocks, which can serve as γ-lactone bioisosteres. The synthetic utility of this approach was further demonstrated by the late-stage transformation of complex biorelevant molecules and the asymmetric transformation of γ-lactam moiety. In practical terms, these synthetic methods hold promise for high-value chemical transformations that can streamline the overall drug discovery process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02673.

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra) (PDF)

Accession Codes

CCDC 1940644, 1940963, 1940966, and 1941110 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hongorg@kaist.ac.kr.
*E-mail: sbchang@kaist.ac.kr.

ORCID

Hoi-Yun Jung: 0000-0003-4111-850X
Sukbok Chang: 0000-0001-9069-0946
Sungwoo Hong: 0000-0001-9371-1730

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported financially by the Institute for Basic Science (IBS-R010-A2). We thank Dr. Dongwook Kim (IBS) for XRD analysis and single-crystal X-ray diffraction experiments with synchrotron radiation were performed at the BL2D-SMC in the Pohang Accelerator Laboratory.

■ REFERENCES

(1) (a) Murphy, S. K.; Dong, V. M. *J. Am. Chem. Soc.* **2013**, *135*, 5553. (b) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213. (c) Wu, X.; Chen, Z.; Bai, Y.-B.; Dong, V. M. *J. Am. Chem. Soc.* **2016**, *138*, 12013. (d) Wang, J.; Zhang, L.; Dong, Z.; Dong, G. *Chem.* **2016**, *1*, 581. (e) Xu, S.; Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 11797.

(2) Miao, Z.; Zhu, L.; Dong, G.; Zhuang, C.; Wu, Y.; Wang, S.; Guo, Z.; Liu, Y.; Wu, S.; Zhu, S.; Fang, K.; Yao, J.; Li, J.; Sheng, C.; Zhang, W. *J. Med. Chem.* **2013**, *56*, 7902.

(3) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.

(4) (a) Baussanne, I.; Schwardt, O.; Royer, J.; Pichon, M.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1997**, *38*, 2259. (b) Krawczyk, H.; Albrecht, Ł.; Wojciechowski, J.; Wolf, W. M.; Krajewska, U.; Różalski, M. *Tetrahedron* **2008**, *64*, 6307. (c) Huang, L.; Wang, S.; Ma, F.; Zhang, Y.; Peng, Y.; Xing, C.; Feng, Y.; Wang, X.; Peng, Y. *Pharmacol. Res.* **2018**, *135*, 201. (d) Cui, L.-Y.; Zhu, Y.-C.; Gao, S.; Wang, J.-M.; Peng, B.; Ni, J.; Zhou, L.-X.; He, J.; Ma, X.-Q. *Chin. Med. J.* **2013**, *126*, 3405.

(5) (a) Toledo, L. M.; Lydon, N. B. *Structure* **1997**, *5*, 1551. (b) Mashhoon, N.; DeMaggio, A. J.; Tereshko, V.; Bergmeier, S. C.; Egli, M.; Hoekstra, M. F.; Kuret, J. *J. Biol. Chem.* **2000**, *275*, 20052.

(6) (a) Spath, E.; Lintner, J. *Ber. Dtsch. Chem. Ges. B* **1936**, *69*, 2727. (b) Kadow, J. F.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1989**, *30*, 3299. (c) Schoenfelder, A.; Mann, A.; Le Coz, S. *Synlett* **1993**,

DOI: 10.1021/acs.orglett.9b02673
Org. Lett. XXXX, XXX, XXX−XXX

1993, 63. (d) Honda, T.; Ishikawa, F.; Kanai, K.; Sato, S.; Kato, D.; Tominaga, H. *Heterocycles* **1996**, *42*, 109. (e) Cui, B.; Yu, J.; Yu, F.-C.; Li, Y.-M.; Chang, K.-J.; Shen, Y. *RSC Adv.* **2015**, *5*, 10386. (f) Xu, J.; Lin, S.; Myers, R. W.; Addona, G.; Berger, J. P.; Campbell, B.; Chen, H.-S.; Chen, Z.; Eiermann, G. J.; Elowe, N. H.; Farrer, B. T.; Feng, W.; Fu, Q.; Kats-Kagan, R.; Kavana, M.; Malkani, S.; McMasters, D. R.; Mitra, K.; Pachanski, M. J.; Tong, X.; Trujillo, M. E.; Xu, L.; Zhang, B.; Zhang, F.; Zhang, R.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2069.

(7) (a) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534. (b) Mishra, N. K.; Oh, Y.; Jeon, M.; Han, S.; Sharma, S.; Han, S. H.; Um, S. H.; Kim, I. S. *Eur. J. Org. Chem.* **2016**, *2016*, 4976. (c) Hermann, G. N.; Bolm, C. *ACS Catal.* **2017**, *7*, 4592. (d) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. *Science* **2018**, *359*, 1016. (e) Zhou, Y.; Engl, O. D.; Bandar, J. S.; Chant, E. D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2018**, *57*, 6672. (f) Hoang, G. L.; Halskov, K. S.; Ellman, J. A. *J. Org. Chem.* **2018**, *83*, 9522. (g) Park, Y.; Chang, S. *Nat. Catal.* **2019**, *2*, 219. (h) Wang, H.; Park, Y.; Bai, Z.; Chang, S.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2019**, *141*, 7194. (i) Xing, Q.; Chan, C.-M.; Yeung, Y.-W.; Yu, W.-Y. *J. Am. Chem. Soc.* **2019**, *141*, 3849. (j) Lei, H.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 2268. (k) Shi, H.; Dixon, D. *J. Chem. Sci.* **2019**, *10*, 3733. (l) Knecht, T.; Mondal, S.; Ye, J.-H.; Das, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2019**, *58*, 7117. (m) Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2019**, *58*, 1153.

(8) (a) Seki, M.; Shimizu, T.; Matsumoto, K. *J. Org. Chem.* **2000**, *65*, 1298. (b) Zhang, C.; Yun, J. *Org. Lett.* **2013**, *15*, 3416. (c) Lohr, T. L.; Li, Z.; Assary, R. S.; Curtiss, L. A.; Marks, T. J. *ACS Catal.* **2015**, *5*, 3675. (d) Zhu, R.; Jiang, J.-L.; Li, X.-L.; Deng, J.; Fu, Y. *ACS Catal.* **2017**, *7*, 7520.

(9) Johnson, A. W.; Gowada, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razavi, Z.; Rosebery, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, *1*, 1734.

(10) Lachia, M.; Wolf, H. C.; Jung, P. J. M.; Screpanti, C.; De Mesmaeker, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2184.

(11) Dangroo, N. A.; Singh, J.; Dar, A. A.; Gupta, N.; Chinthakindi, P. K.; Kaul, A.; Khuroo, M. A.; Sangwan, P. L. *Eur. J. Med. Chem.* **2016**, *120*, 160.

(12) (a) Topcu, G.; Ulubelen, A.; Tam, T. C.-M.; Che, C.-T. *J. Nat. Prod.* **1996**, *59*, 113. (b) Dixon, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 8432. (c) Zhang, W.; Yao, H.; Yu, J.; Zhang, Z.; Tong, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 4787. (d) Menger, M.; Lentz, D.; Christmann, M. *J. Org. Chem.* **2018**, *83*, 6793. (e) Jasiński, M.; Stukkens, Y.; Degand, H.; Purnelle, B.; Marchand-Brynaert, J.; Boutry, M. *Plant Cell* **2001**, *13*, 1095.

(13) Filippakopoulos, P.; Qi, J.; Picaud, S.; Shen, Y.; Smith, W. B.; Fedorov, O.; Morse, E. M.; Keates, T.; Hickman, T. T.; Felletar, I.; Philpott, M.; Munro, S.; McKeown, M. R.; Wang, Y.; Christie, A. L.; West, N.; Cameron, M. J.; Schwartz, B.; Heightman, T. D.; Thangue, N. L.; French, C. A.; Wiest, O.; Kung, A. L.; Knapp, S.; Bradner, J. E. *Nature* **2010**, *468*, 1067.

(14) Discovery Studio 2019 software was used for the docking simulation.

(15) Sam, K. M.; Auger, S.; Luu-The, V.; Poirier, D. *J. Med. Chem.* **1995**, *38*, 4518.

(16) IC_{50} determinations were performed at Reaction Biology Corp.

DOI: 10.1021/acs.orglett.9b02673
Org. Lett. XXXX, XXX, XXX−XXX