Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

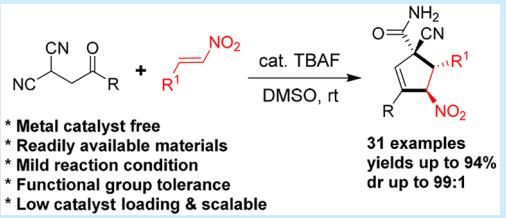
One-Step, Effective, and Cascade Syntheses of Highly Functionalized Cyclopentenes with High Diastereoselectivity

Suman Alishetty, Hong-Pin Shih, and Chien-Chung Han*

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan, ROC

Supporting Information

ABSTRACT: Tetrabutylammonium fluoride works as an effective organocatalyst for the cycloaddition between phenacylmalononitriles and electron-deficient olefins (having substituent groups of NO_2, CHO, and COR), providing a facile synthetic route to versatile multifunctionalized cyclopentenes having an allylic quaternary carbon center bearing both cyano and carboxamide groups with high yields and high diastereoselectivity. Preliminary studies reveal that these functionalized cyclopentenes are convenient precursors for making α-cyano-functionalized cyclopentadienone oximes.



Highly functionalized cyclopentenes are valuable structural motifs for many bioactive and medicinal compounds,[1,2] such as (−)-carbovir,[3a] *trans*-α-necrodyl isobutyrate,[3b] laurokamurene A,[3c] (−)-lycoposerramine-R,[3d] and tetrahydropyranal cyclopentyl benzylamide (TCB) derivatives[4] (see Supporting Information (SI) Figure S1). TCB derivatives, having a functionalized cyclopentene core with a preferable allylic quaternary carbon center with a carboxamide and another electron-withdrawing group (such as CN, halogen, ester, CF_3, sulfonyl, heterocycles, etc.), may serve as modulators for chemokine receptor activity[4a,b] and may be useful in the prevention/treatment of certain immune regulatory disorders. Furthermore, a series of small amphipathic $\beta^{2,2}$-amino acid derivatives[5] having a quaternary carbon center with a carboxamide and a β-amino group (which was converted from an α-cyano group via reduction) are found to be a promising new class of anticancer agents. Quite a few strategies[6a−d] have been reported for the synthesis of multifunctionalized cyclopentene (CP) derivatives. While, only limited examples have been reported for making functionalized CP containing a quaternary carbon center with both cyano and carboxamide groups from (a) a malononitrile, followed by double α-allylation, ring-closure metathesis, and enzyme-differentiated hydrolysis;[6e] (b) a cyanoesteramide, followed by double α-allylation and then ring-closure metathesis;[6f] and (c) a cyanoesteramide plus an asymmetric allenoate to undergo a phosphine-catalyzed [4 + 1] annulation.[6g] However, these methodologies require expensive catalysts (e.g., transition metal catalyst,[6e,f,i] organocatalyst,[6g,i] and enzyme[6e]) or reactive reagent[6f] and are only applicable for limited substrate scope.[6e−g] Furthermore, they only provided the functional quaternary carbon at the β-position to the vinyl group, instead of at the desirable allylic position of the CP core. Therefore, development of viable synthetic methods for making CPs having an allylic quaternary carbon bearing both cyano and carboxamide groups is still needed. Herein, we report a facile one-step and effective synthetic method for making such highly functionalized cyclopentenes with high yields and high diastereoselectivities.

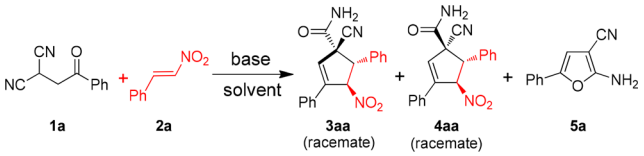
Previously, we demonstrated that a catalytic amount of TBAF can work as an effective base to catalyze the C−C bond formation via Michael addition between active methylene groups (such as those in malononitrile, nitromethane, etc., as the Michael donors) and a diiminoquinoid ring (as the Michael acceptors).[7] In those reactions, the fluoride works as an effective base to activate the Michael donors via the α-H abstraction, forming HF, which in turn works as an effective acid to activate the Michael acceptor by protonating its imino group.

In this work, we further conceived that the dual functional organocatalyst TBAF might be useful in promoting a cascade Michael reaction between a strong Michael acceptor and a dual functional compound, such as phenacylmalononitrile (**1a**) that contains both a Michael donor moiety and a less reactive Michael acceptor moiety, to form a five-membered carbocyclic ring. Our first attempt was performed by reacting **1a** with 1 equiv of *trans*-β-nitrostyrene (**2a**) at rt in the presence of 5 mol % of TBAF in THF (entry 1, Table 1). The reaction was completed in 5 h to form cyclic diastereomers of **3aa** (68%, racemate) and **4aa** (20%, racemate) and a highly substituted furan **5a**[8] (7%) (see the equation in Table 1). Racemate formation for **3a** (as in **3aa** and **3ad**) and **4a** (as in **4ad**) compounds was further confirmed by the single-crystal X-ray crystallography diffraction data (see SI) and the inability to show net rotation of plane-polarized light by the respective compounds. As revealed by the structures, the 4-nitro group is *trans* to the carboxamide functional group in **3aa** but *cis* in **4aa**. The *cis* configuration in **4aa** allows its carboxamide to be H-bonded with the nitro groups, which is accountable for the more downfield NH_2 peak in **4aa** (at δ 8.06) compared to that in **3aa** (at δ 7.58) (see SI Figure S2). The NMR NOE results for **3aa**

Received: February 11, 2018

DOI: 10.1021/acs.orglett.8b00510
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Solvent and Base Effects on the Reaction of 1a and 2a



entry[a]	base (mol %)	solvent	time (h)	ratio (3aa/4aa)[b]	3aa (%)[c]
1	TBAF (5)	THF	5.0	76:24	68
2	TBAF (5)	MeOH	5.0	50:50	44
3	TBAF (5)	EtOH	5.0	50:50	42
4	TBAF (5)	*i*-PrOH	5.0	60:40	67
5	TBAF (5)	*n*-BuOH	5.0	74:26	60
6	TBAF (5)	CH_3CN	5.0	79:21	72
7	TBAF (5)	DMF	5.0	91:9	87
8	TBAF (5)	DMSO	5.0	98:2	89
9	TBAF (100)	DMSO	1.0	95:5	85
10[d]	KF (100)	DMSO	1.0	82:18	67
11[d]	CsF (100)	DMSO	1.0	89:11	79
12[d]	KHF_2 (100)	DMSO	1.0	83:17	62
13[f]	TBAC (100)	DMSO	24		trace
14[f]	TBAB (100)	DMSO	24		trace
15[f]	DBU (30)	DMSO	1.0	58:42	43
16	Et_3N (100)	DMSO	1.0	50:50	37
17[d]	K_2CO_3(100)	DMSO	1.0	51:49	35
18	NaOH (100)	DMSO	1.0	*e*	17
19	no base	DMSO	24		ND

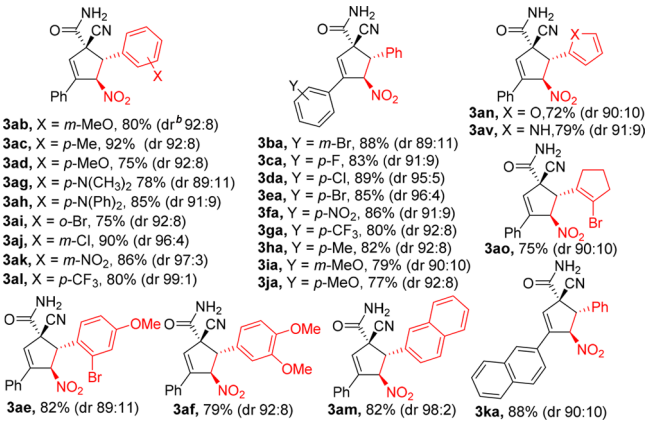
[a][Substrate] = 0.54 M; the yields of byproduct **5a** were found to be 5−10% in general. [b]Diastereomeric ratio was determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield after column chromatography; ND (not detected). [d]Bases were partially soluble in DMSO. [e]Product mixture was too complicated to be correctly estimated. [f]TBAC (tetrabutylammonium chloride); TBAB (tetrabutylammonium bromide); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

and **4aa**, as summarized in SI Scheme S1, are also consistent with their respective steric structures.

To find the optimal reaction conditions and understand the nature of the diastereoselectivity, model studies using **1a** and **2a** with TBAF (5 mol %) were performed in various solvents at room temperature, and the results are summarized in Table 1 (entries 1−8). Interestingly, when protic solvents were used, such as MeOH (ε = 33), EtOH (ε = 25), *i*-PrOH (ε = 17.9), and *n*-BuOH (ε = 17), the diastereoselectivity clearly decreased as the polarity (i.e., dielectric constant ε) of the protic solvent medium increased (entries 2−5, Table 1). In the aprotic solvents, such as THF (ε = 7.8), CH_3CN (ε = 38), DMF (ε = 37), and DMSO (ε = 47), the diastereoselectivity actually increased as the polarity of the aprotic solvent increased (entries 1 and 6−8, Table 1). In the most polar aprotic solvent, such as DMSO (ε = 47), the reaction gave the best isolated yield of **3aa** (89%) with the highest diastereoselectivity (98:2; as estimated by ^{1}H NMR). The mechanistic implications for these contradicting solvent effects will be further discussed below. Regarding the base effects, the studies were conducted using the same reactants (**1a** and **2a**) in DMSO with various bases (1 equiv) at rt, and the results are summarized in Table 1 (entries 9−19). As expected, in the absence of any base, the control experiment (Table 1, entry 19) failed to promote any reactions. The results clearly indicated that a fairly high diastereoselectivity of **3aa**/**4aa** (>82:18) can always be obtained (entries 9−12) as long as a fluoride base was used, despite their originality (TBAF, KF, CsF, or KHF_2), but TBAF (entry 9, Table 1) still gave the best yield (85%) and the highest diastereoselectivity (95:5), probably due to its high solubility. Although TBAC and TBAB contain the same tetrabutylammonium (TBA) cation like TBAF, they however failed to promote any reaction (entries 13 and 14, Table 1) even up to 24 h. Thus, it is the fluoride anion and not the TBA cation that is responsible for the high reactivity and diastereoselectivity. Other stronger bases like DBU, NEt_3, and K_2CO_3 gave essentially no or very poor diastereoselectivity (Table 1, entries 15−17). Regarding the case of NaOH (entry 18), its undesired strong basicity led to the formation of a very complicated product mixture, which dramatically reduced the isolable yield of **3aa** (17%) and made the isolation of pure **4aa** impossible. The above results clearly indicated that a nonsolvated fluoride anion plays the key roles for the reactivity and the stereoselectivity for the cycloaddition between **1a** and **2a**.

To check the effective substrate scope of the reaction, systematic studies were performed with TBAF (5 mol %) in DMSO at rt using either the combination of **1a** and different substituted reactants **2** or the combination of different substituted reactants **1** and **2a**. The results (Scheme 1) revealed

Scheme 1. Applicable Substrate Scopes Based on the Electron-Deficient Nitrostyrenes and Phenacylmalononitriles[a]



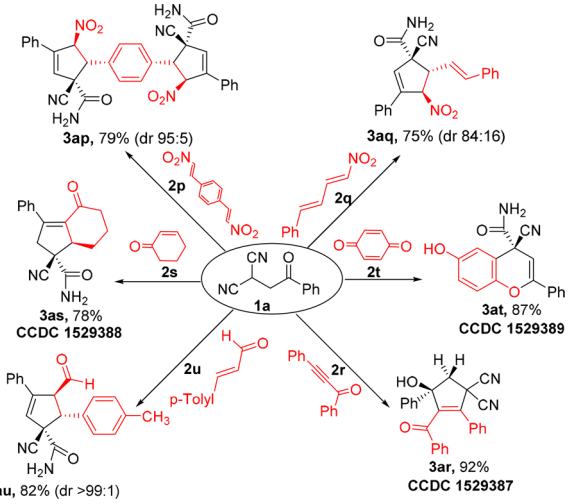
[a]Reactions were performed on a 0.27 mmol scale. [b]All yields correspond to isolated yields with dr as determined by ^{1}H NMR of the crude mixture.

that the reactions gave, in general, high yields and high diastereoselectivities, despite the electronic nature of the substituents on either of the aryl rings. Apparently, the activation effect of the fluoride is far more important than the electronic effects of the substituent. Other aryl or vinyl groups, such as naphthyl, furyl, and 2-bromocyclopentenyl, were also working well.

This synthetic method is also applicable for multifunctional nitrostyrene (e.g., **2p**) and the conjugation extended nitrostyrene (e.g., **2q**). Likewise, it is also expandable to other electron-deficient alkene or alkyne systems, such as α,β-unsaturated ketones (e.g., ynone **2r**, cyclopehexenone **2s**, 1,4-benzoquinone **2t**) and α,β-unsaturated aldehyde (e.g., 4-methylcinnamaldehyde, **2u**) (Scheme 2). Interestingly, when **1a** reacts with ynone **2r**, it forms a cyclopentenol (instead of a cyclopentene) with the concurrent preservation of the dicycano group (see X-ray crystallography result in SI). The results suggest that the formation of the carboxamide group and the loss of the hydroxyl group (which originated from the carbonyl group of **1a**) in all other cases are tightly linked events.

DOI: 10.1021/acs.orglett.8b00510
Org. Lett. XXXX, XXX, XXX−XXX

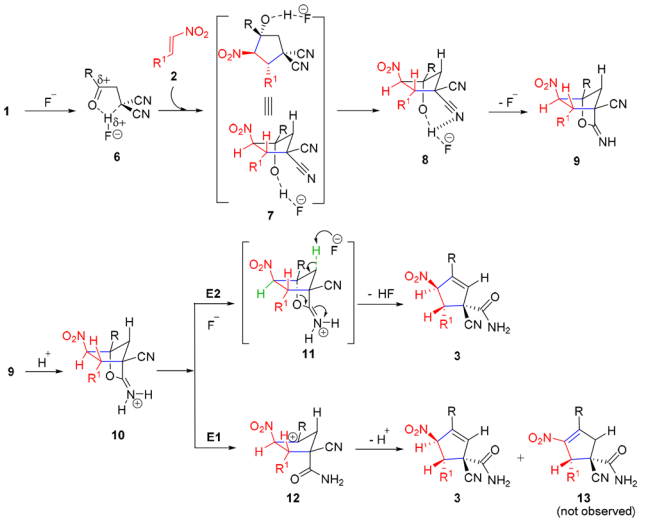
Scheme 2. Extended Synthetic Applications with Other Electron-Deficient Olefins[a]



[a]Reactions were performed on a 0.27 mmol scale. All yields correspond to isolated yields with dr as determined by ^{1}H NMR of the crude mixture.

Based on the above experimental results, a plausible reaction mechanism is proposed in Scheme 3 to account for the preferable

Scheme 3. Plausible Formation Mechanism for the Diastereomer 3[a]



[a]Electron-rich cyclopentene **3** is more stable than the electron-deficient cyclopentene **13** by 3.2 kcal/mol, according to the gas-phase DFT calculation at the B3LYP/6-31G(d) level with Gaussian 09 (as depicted in SI Scheme S2).

formation of diastereomer **3**. Apparently, the fluoride anion is the major activator and the key controller for the diastereoselectivity. Thus, the activation might be started with the H-bonding interaction between fluoride and the most acidic and positively charged H (i.e., the α-H of the malononitrile group). Such H-bonding interactions could further increase the ionization degree and the acidity of α-C−H and render it active enough to coordinate with the γ-carbonyl group, forming a five-membered ring, adduct **6**. Adduct **6** containing both an activated nucleophilic center (i.e., the α-C) and an activated electrophilic center (i.e., the γ-carbonyl group) should be active enough to undergo fast reaction with **2** via a cascade of two consecutive Michael additions to form a stereospecific cyclopentanol intermediate **7** (i.e., 4-hydroxy-3-nitro-2,4-diphenylcyclopentane-1,1-dicarbonitrile), with the nitro and the R^1 groups (both originated from nitrostyrene **2**) being retained in a 1,2-*trans* configuration, as expected for a fast concerted cyclization reaction between the two molecules. In this hypothetical intermediate **7**, the R^1 (originated from **2**) and R (originated from **1**) would be preferably arranged in a 1,3-*trans* configuration due to the need to minimize the steric hindrance interaction as the nitrostyrene approaches adduct **6** for cyclization. Such a steric requirement would render the newly formed hydroxy group (still H-bonded with the fluoride anion) to be *trans* to the nitro group, as depicted in **7**.

Likewise, the H-bonding with a fluoride would help increase the acidity of the O−H group in **7**, which, in turn, would increase its ability to activate the nearby *cis*-cyano group (i.e., the CN *trans* to the nitro) via protonation (or H-bonding interaction) to enable a fast intramolecular nucleophilic addition between the hydroxy and the *cis*-cyano group, resulting in a bicyclic intermediate **9** (2-oxabicyclo[2.2.1]heptan-3-imine). The fast conversion from the hypothetical intermediate **7** to **9** can be confirmed by the experimental observations that no cyclopentene or cyclopentanol with the original dicyanomethylene moiety (the potential products that could be derived from **7**) has ever been observed. It is conceivable that bicyclic intermediate **9** could be easily further activated via protonation at the basic imino group (most likely by HF) to form a 2-oxabicyclo[2.2.1]-heptan-3-iminium cation **10**, which could then be converted to the final product **3** via either an E2 elimination pathway (possibly, through the depicted transition state **11** and being assisted by a fluoride base) or an E1 elimination pathway (possibly through a tertiary benzylic cation **12**).

When the reaction was carried out with a stronger base (e.g., NEt_3, K_2CO_3, and NaOH), the base might have abstracted the α-H from the malononitrile group of substrate **1** to form a conventional anionic nucleophile **14** (1,1-dicyano-3-oxo-3-phenylpropan-1-ide), which might then react with **2** via a conventional stepwise Michael addition mechanism, leading to a pair of diastereomers **3** and **4** with poor selectivity (see SI Scheme S4).

Although more rigorous studies are still needed to finalize the actual mechanism, the current proposal can help explain the unusual contradicting solvent effects on the diastereoselectivity. In aprotic solvents (e.g., DMSO, DMF, CH_3CN, and THF), the solvents with higher dielectric constants can better polarize the α-C−H bond, thus facilitating formation of adduct **6** and increasing the selectivity. In the protic solvents (e.g., *n*-BuOH, *i*-PrOH, EtOH and MeOH), the solvents with higher dielectric constants would have a stronger solvation interaction with the fluoride and thus reduce the concentration of adduct **6** and lower the selectivity.

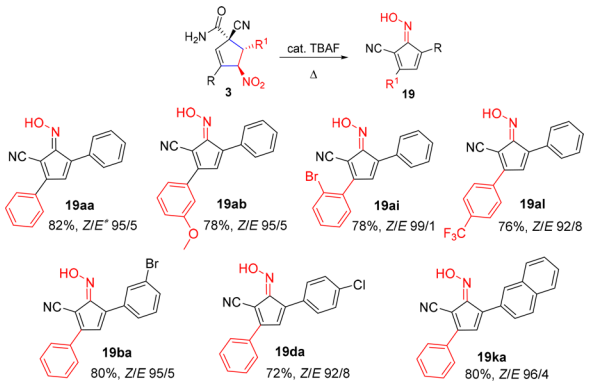
This mechanistic rationale actually prompts us to check the H_2O (which is a protic solvent with the highest dielectric constant) impurity effect. When the same reaction (entry 8, Table 1) of **1a** and **2a** was repeated in freshly purchased anhydrous DMSO (ACS grade; Merck; H_2O content <0.025%), the diastereoselectivity of **3aa** became quantitative (SI Figure S3b). On the other hand, when the same reaction was carried out in a cosolvent of DMSO/H_2O (90/10), the diastereoselectivity disappeared totally (SI Figure S3c). Likewise, when the syntheses of **3ac**, **3ai**, **3ag**, **3ba**, and **3ia** were also repeated in anhydrous

DOI: 10.1021/acs.orglett.8b00510
Org. Lett. XXXX, XXX, XXX−XXX

DMSO solvent, their diastereoselectivities were all clearly increased (SI Table S1). More detailed studies for the H_2O impurity effect are underway.

Interestingly, we found that the multifunctionalized cyclopentene **3** can be further easily transformed into a multifunctionalized cyclopentadienone oxime **19** (Scheme 4), with

Scheme 4. Formation of (*Z*)-5-(Hydroxyimino)-2,4-diarylcyclopenta-1,3-diene-1-carbonitrile 19[a]



[a]Reactions were performed on a 0.27 mmol scale. All yields correspond to isolated yields with *Z*/*E* isomer ratio as determined by ^{1}H NMR of the crude mixture.

assistance of catalytic TBAF at increased temperatures under appropriate reaction conditions (see X-ray crystallography data for **19aa** and **19ai** in SI). It is worth noting that the core cyclopentadienone−oxime structures of these compounds can be often found in many bioactive molecules as the modulators for peroxisome proliferated activated receptor.[9] Further detailed studies about these novel transformation reactions are underway.

In conclusion, we successfully developed a new and effective method for the synthesis of a wide variety of multifunctionalized cyclopentenes. The reaction proceeds well under mild conditions to give highly diastereoslective compounds and can tolerate both the electron-donating and electron-withdrawing substituents on the substrates. Moreover, these highly functionalized cyclopentenes can serve as the precursors for making highly functionalized cyclopentadienone oximes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00510.

Experimental procedures and characterization of products (PDF)

Accession Codes

CCDC 1045321−1045322, 1529387−1529389, 1585449, 1816533, and 1817817 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 Author

*E-mail: cchan@mx.nthu.edu.tw.

ORCID

Chien-Chung Han: 0000-0002-1045-0270

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support from the Ministry of Science and Technology, Republic of China.

■ REFERENCES

(1) (a) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, N. *Chem. Rev.* **2007**, *107*, 3286−3337. (b) Seemann, M.; Schöller, M.; Kudis, S.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, *2003*, 2122−2127. (c) Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2756−2760.

(2) (a) Kim, K. H.; Miller, M. J. *Tetrahedron Lett.* **2003**, *44*, 4571−4573. (b) Chebib, M.; Duke, R. K.; Allan, R. D.; Johnston, G. A. R. *Eur. J. Pharmacol.* **2001**, *430*, 185−192. (c) Liu, G.; Shirley, M. E.; Van, K. N.; McFarlin, R. L.; Romo, D. *Nat. Chem.* **2013**, *5*, 1049−57.

(3) (a) Parker, W. B.; Shaddix, S. C.; Bowdon, B. J.; Rose, L. M.; Vince, R.; Shannon, W. M.; Bennett, L. L., Jr. *Antimicrob. Agents Chemother.* **1993**, *37*, 1004−1009. (b) Figadère, B. A.; McElfresh, J. S.; Borchardt, D.; Daane, K. M.; Bentley, W.; Millar, J. G. *Tetrahedron Lett.* **2007**, *48*, 8434−8437. (c) Srikrishna, A.; Beeraiah, B.; Ramesh Babu, R. *Tetrahedron: Asymmetry* **2008**, *19*, 624−627. (d) Ishida, H.; Kimura, S.; Kogure, N.; Kitajima, M.; Takayama, H. *Tetrahedron* **2015**, *71*, 51−56.

(4) (a) Gabor, B.; Mills, S. G.; Pasternak, A.; Shankarnan, K.; Yang, L.; Zhou, C.; Globe, S. D. WIPO Patent Appl. WO 2004/041161A2, 2004. (b) Nair, A. G.; Kozlowski, J. A. U.S. Patent Appl. US 2013/0345254 A1, 2013.

(5) (a) Hansen, T.; Ausbacher, D.; Zachariassen, Z. G.; Anderssen, T.; Havelkova, M.; Strøm, M. B. *Eur. J. Med. Chem.* **2012**, *58*, 22. (b) Hansen, T.; Ausbacher, D.; Flaten, G. E.; Havelkova, M.; Strøm, M. B. *J. Med. Chem.* **2011**, *54*, 858.

(6) (a) Wei, Y.; Shi, M. *Org. Chem. Front.* **2017**, *4*, 1876−1890 and references therein. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336−5346. (c) Tian, J.; He, Z. *Chem. Commun.* **2013**, *49*, 2058−60. (d) Leemans, E.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2011**, *111*, 3268−3333. (e) Vink, M. K. S.; Wijtmans, R.; Reisinger, C.; van den Berg, R. J. F.; Schortinghuis, C. A.; Schwab, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Biotechnol. J.* **2006**, *1*, 569 and references therein. (f) Xu, L. W.; Gao, P. S.; Li, N.; Zhang, J. L.; Zhu, Z. L.; Gao, Z.-W.; Sun, H. M.; Zhang, W. Q. *ChemCatChem* **2016**, *8*, 3466−3474. (g) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183−13187. (h) Zhang, H. J.; Meng, T.; Demerseman, B.; Bruneau, C.; Xi, Z. *Org. Lett.* **2009**, *11*, 4458−4461. (i) Blom, J.; Vidal-Albalat, A.; Jørgensen, J.; Barløse, C. L.; Jessen, K. S.; Iversen, M. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 11831−11835 and references therein.

(7) Paike, V. V.; Balakumar, R.; Chen, H. Y.; Shih, H. P.; Han, C. C. *Org. Lett.* **2009**, *11*, 5586−5589.

(8) Han, J.; Kaspersen, S. J.; Nervik, S.; Nørsett, K. G.; Sundby, E.; Hoff, B. H. *Eur. J. Med. Chem.* **2016**, *119*, 278−299 and references therein.

(9) (a) Tseng, C. H.; Tung, C. W.; Wu, C. H.; Tzeng, C. C.; Chen, Y. H.; Hwang, T. S.; Chen, Y. L. *Molecules* **2017**, *22*, 1001. (b) Cheon, H. G.; Yoo, S. E.; Kim, S. S.; Yang, S. D.; Kim, K. R.; Rhee, S. D.; Ahn, J. H.; Kang, S. K.; Jung, W. H.; Park, S. D.; Kim, N. G.; Lee, J. H.; Huh, S. C.; Lee, J. M.; Song, S. B.; Kwon, S. J.; Kim, J. H.; Lee, J. H.; Kim, S. J. PCT Int. Appl. WO2005/100303 A1, 2005.

DOI: 10.1021/acs.orglett.8b00510
Org. Lett. XXXX, XXX, XXX−XXX