Accepted Manuscript

The application of Morita-Baylis-Hillman reaction: Synthetic studies on perophoramidine

Lin Wu, Qian-Ru Zhang, Ji-Rong Huang, Yang Li, Fu Su, Lin Dong

PII: S0040-4020(17)30568-9

DOI: 10.1016/j.tet.2017.05.067

Reference: TET 28733

To appear in: *Tetrahedron*

Received Date: 6 April 2017

Revised Date: 17 May 2017

Accepted Date: 19 May 2017

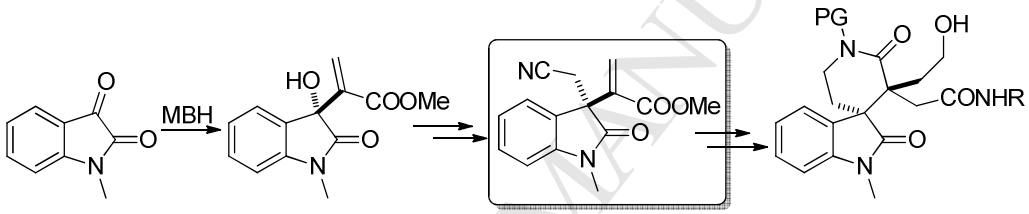
Please cite this article as: Wu L, Zhang Q-R, Huang J-R, Li Y, Su F, Dong L, The application of Morita-Baylis-Hillman reaction: Synthetic studies on perophoramidine, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.05.067.

Graphical Abstract

The application of Morita-Baylis-Hillman reaction: synthetic studies on perophoramidine

Lin Wu,[a] Qian-Ru Zhang,[a] Ji-Rong Huang,[a]
Yang Li,[a] Fu Su,[a,*] and Lin Dong[a,*]
[a]*Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu 610041,China*

A new concise methodology was developed for the synthesis of the two vicinal quaternary centers of the natural product perophoramidine. Key steps involved the Morita-Baylis-Hillman reaction, reductive cyclization and allylic alkylation. Moreover, most conditions are simple and convenient with good yields.



Tetrahedron
journal homepage: www.elsevier.com

The application of Morita-Baylis-Hillman reaction: synthetic studies on perophoramidine

Lin Wu,[a] Qian-Ru Zhang,[a] Ji-Rong Huang,[a] Yang Li,[a] Fu Su,[a,*] and Lin Dong[a,*]

[a] *Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu 610041,China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Vicinal quaternary centers
MBH
Reductive cyclization
Allylic alkylation

ABSTRACT

A new concise methodology was developed for the synthesis of the two vicinal quaternary centers of the natural product perophoramidine. Key steps involved the Morita–Baylis–Hillman reaction, reductive cyclization and allylic alkylation. Moreover, most conditions are simple and convenient with good yields.

1. Introduction

In 2002, Ireland and co-workers reported the isolation of perophoramidine from the Philippine ascidian organism Perophoranamei, and this architecturally intriguing natural product possesses cytotoxicity toward HCT116 colon carcinoma cells (IC_{50} = 60 μM).[1] With use of multidimensional NMR techniques, the striking molecular structure of perophoramidine is characterized by its complex densely functionalized hexacyclic system with two crucial vicinal all-carbon quaternary stereocenters, the skeletal connectivity of which is related to the Penicillium derived communesin alkaloids (Figure 1).[2]

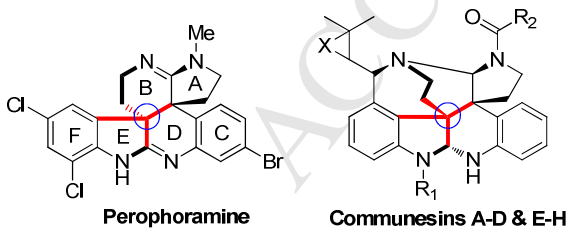


Figure 1. Structures of Perophoramidine and Communesins

By virtue of the appealing biological activities and challenging structures, perophoramidine has attracted an attention of synthetic organic chemists in recent years.[3-8] The first total synthesis of (±)-perophoramidine was reported by Funk, which employed hetero Diels–Alder reaction as a key step.[3] Rainier developed a new spiro cyclization reaction to generate (±)-dehaloperophoramidine.[4] Subsequently, the asymmetric biomimetic Diels–Alder reaction has been used by Qin to first total synthesis of (+)-perophoramidine.[5] Recently, Wang achieved the total synthesis of (+)-perophoramidine using a nickel(II)-catalyzed asymmetric alkylation reaction.[6] Trost utilized a molyndenum-catalyzed asymmetric allylic alkylation to crate (-)-perophoramidine.[7]

Recently, Morita–Baylis–Hillman (MBH) reaction has emerged as a very versatile tool to deliver multifunctional compounds.[9] Toward a unique synthetic strategy distinct from the reported strategies, we envisioned our efforts towards the synthesis of perophoramidine core structure via a key MBH reaction as the starting response, which might construct the pivotal quaternary center at the first step.

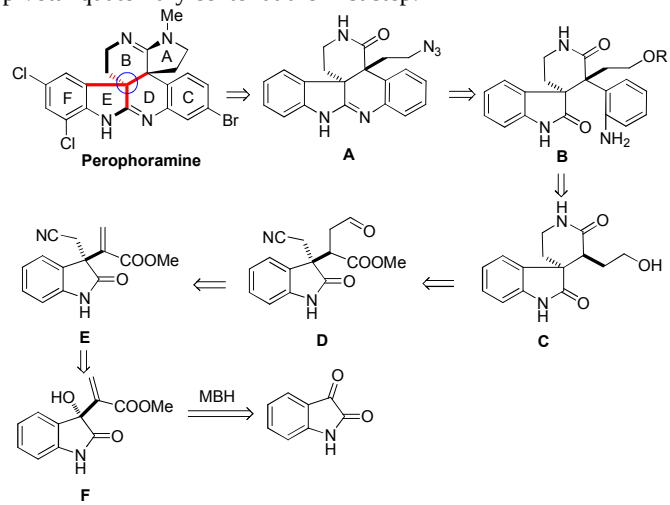
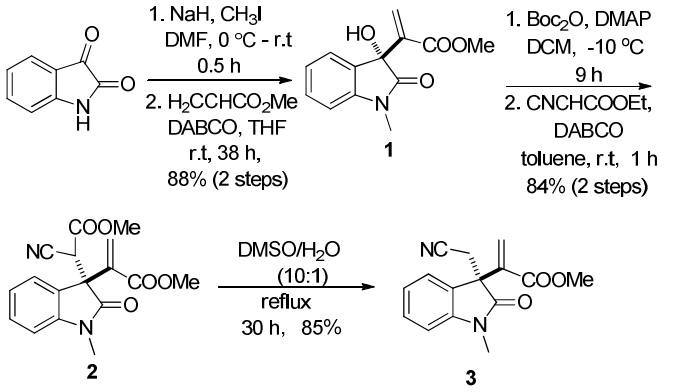


Figure 2. Retrosynthetic synthesis of Perophoramidine

* Corresponding author. Tel.: +86-28-85503538; e-mail: dongl@scu.edu.cn

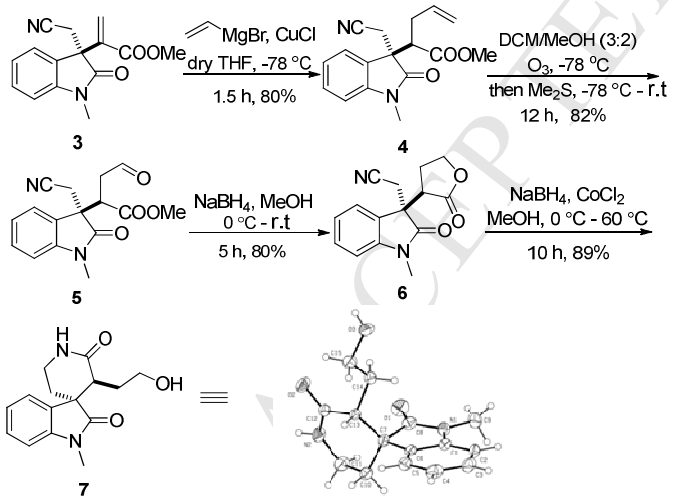
As depicted in Figure 2, we expected that the target perophoramidine could be synthesized from the azide compound **A** via formation of the A ring. The compound **A** could be generated from spiro lactam intermediate **C** via arylation reaction and condensation. Reductive cyclization of aldehyde compound **D** could deliver the lactam compound **C**. The requisite aldehyde compound **D** could be obtained from the isatin via Morita-Baylis-Hillman reaction.

2. Results and discussion



Scheme 1. Synthesis of cyano compound **3** via MBH reaction

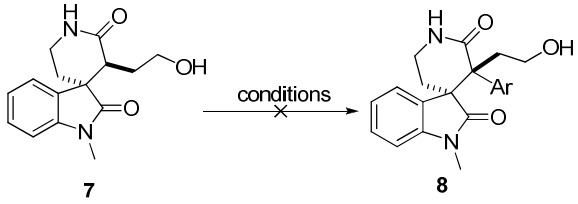
Firstly, we set out to investigate whether the key intermediate quaternary carbon compound **3** could be built via MBH reaction (Scheme 1). It was found that MBH reaction as a means could really proceed well to afford the tertiary alcohol **1** from commercially available isatin, which then followed by Boc protection and nucleophilic elimination reaction providing product **2**. Subsequently, **2** went through decarboxylation to give the desired quaternary center intermediate **3**. It is worth noting that the nitrogen in isatin had to be protected first with methyl group, otherwise key intermediate **3** can't be obtained.



Scheme 2. Synthesis of the spiro-fused oxoindolin **7**

As we expected, 1,4-addition of **3** worked smoothly with vinyl Grignard reagent under the established reaction conditions, generating terminal alkenyl **4** in 80% yield. After oxidation of alkenyl group by O_3 and then reduction in the presence of $NaBH_4$, the resultant alcohol underwent intramolecular ester exchange to yield lactone compound **6**, which was subjected to reduction and subsequent amine ester exchange to deliver important spiro-fused oxoindolin **7**, whose structure was established by X-ray analysis (Scheme 2).[10]

Table 1.
The exploration of arylation reaction to form **8**[a]

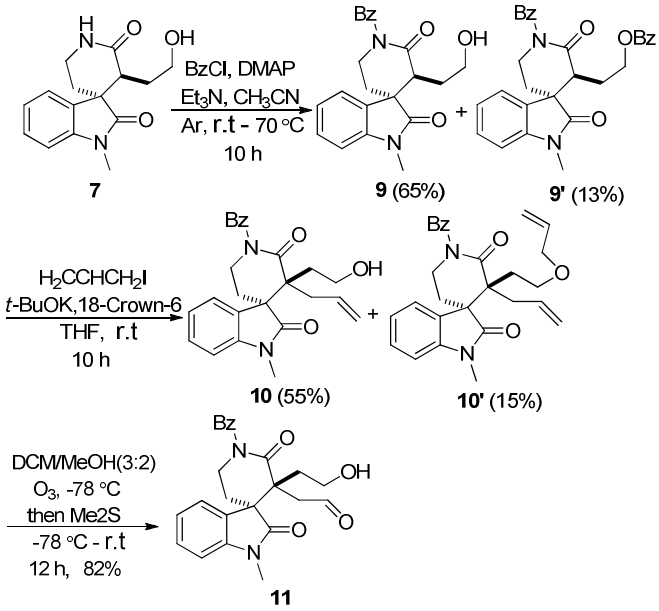


Entry	Aryl halide	Base	Ligand	Solvent	Result
1	2-iodoaniline	KHMDS	-	THF	Mess[b]
2	2-iodoaniline	LiHMDS	dppf	THF	Mess[b]
3	1-bromo-2-iodobenzene	KHMDS	-	MeCN	Mess[b]
4	1-bromo-2-iodobenzene	LiHMDS	dppf	MeCN	Mess[b]

[a] All reaction conditions unless otherwise specified: 0.1 mmol of **7**, 0.15 mmol of aryl halide, 0.3 mmol of base, 5 mol % of $Pd(dba)_2$, 0.2 mmol of $ZnCl_2$, 1 mL of solvent, reflux, 36 h, under argon atmosphere.
[b] Aryl halide was homocoupling and **7** was decomposed.

With **7** in hand, we next examined the construction of the D ring. To achieve this goal, we settled upon various arylation reactions to establish the second quaternary carbon center.[11] Unfortunately, the approaches using 2-iodoaniline or 1-bromo-2-iodobenzene as the source of aromatic groups were all failed (Table 1).

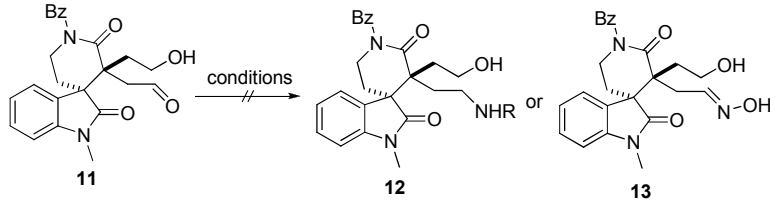
In view of above result, we decided to change the target and keep on studying the analogue of perophoramidine skeleton. Therefore, we then speculated to build the second quaternary center via allylation reactions (Scheme 3). To our surprise, only benzoyl chloride as a protecting agent could protect the amide, giving the Bz protection of the lactam **9** together with O-protection product **9'** in good yield.[11] Allylation of Bz protection product **9** gave a single alkylation product **10** and less amount of **10'**. The desired oxidation product **11** was performed through ozonation sequence from alkenyl compound **10**.



Scheme 3. Synthesis of the spiro compound **11**

Table 2.

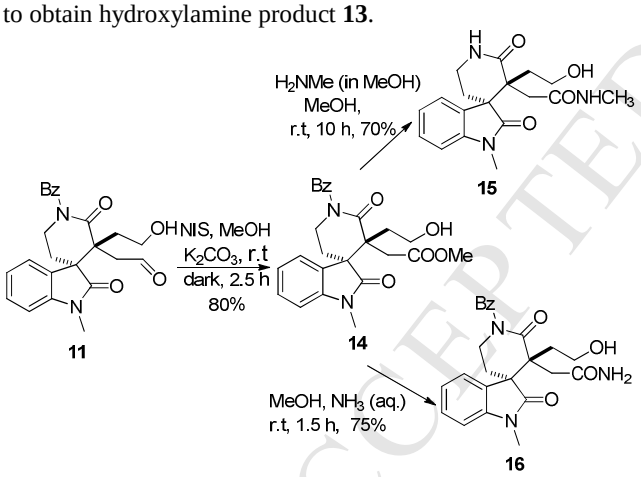
The exploration of aromatization reaction to form **8**[a]



Entry	Amine	Acid	Base	Reductive agent	Desiccant	Temp. /°C	Solvent	Result
1	H_2NMe	TsOH	-	$NaBH_4$	-	0-30	Toluene	Decomposed
2	$BnNH_2$	$Ti(OiPr)_4$	-	$NaBH_4$	$MgSO_4$	30	THF	Decomposed
3	$BnNH_2$	$NaBH(OAc)_3$	-	$NaBH_4$	-	0-30	CH_2Cl_2	Decomposed
4	$BnNH_2$	TsOH	-	$NaBH_4$	-	0-120	Toluene	Decomposed
5	NH_3	AcOH	-	$NaBH_4$	$MgSO_4$	0-75	THF	Decomposed
6	H_2N-Boc	TsOH	-	$NaCNBH_3$	-	0-110	THF	Decomposed
7	$BnNH_2$	-	-	$NaBH_3CN$	-	30-70	AcOH	Decomposed
8	NH_4OAc	-	Et_3N	Al_2Te_3	-	50	THF/H_2O	Trace
9	$BnNH_2$	AcOH	-	Pd/H_2	-	100	THF	Trace
10	H_2N-OH	-	E_3N	LAH	$MgSO_4$	0-75	THF	Decomposed
11	H_2N-OH	-	NaOH	-	-	30	THF	Trace
12	H_2N-OH	-	NaOH (40% aq)	-	-	30	MeOH	Trace
13	H_2N-OH	-	$NaHCO_3$	-	-	30	$EtOH/H_2O$ (1:1)	Trace
14	H_2N-OH	-	Na_2CO_3	-	-	30	THF/H_2O (1:1)	Trace
15	H_2N-OH	-	AcONa	-	-	80	EtOH	Trace
16	H_2N-OH	-	Py	-	-	30	THF/H_2O (3:2)	Trace

[a] All reaction conditions unless otherwise specified: 0.1 mmol of **11**, 0.15 mmol of amine, 0.15 mmol of acid, 0.2 mmol of base, 0.5-0.7 mmol of reductive agent, 0.12 mmol of desiccant, 1 mL of solvent, 12 h.

At this stage, we tried to convert the aldehyde group into an amine, and further synthesizing the D ring.[11] However, after a lot of experiments, we couldn't get the desired aminated product **12** (Table 2). Unfortunately, these conditions were also no working to obtain hydroxylamine product **13**.

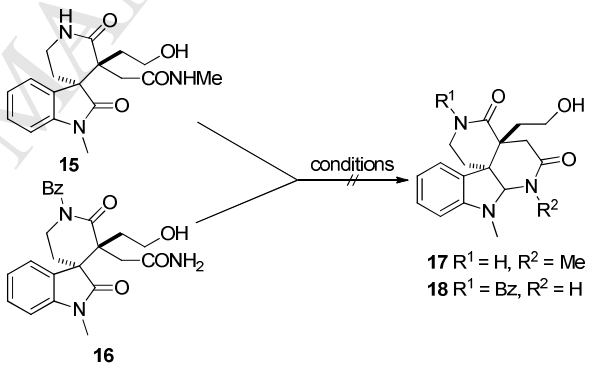


Scheme 4 Synthesis of amide compounds **15** and **16**

After that, we wanted to convert the aldehyde group to the amide and then to synthesize the D ring by using the Zhou's conditions.[12] In this instance, on exposure to potassium carbonate and NIS, aldehyde **11** underwent oxidation to furnish esterification product **14**, which could be involved in the similar amine ester exchange process to lead the amide products **15** and **16** (Scheme 4). Worthy of note, however, is the failure of amide **15** or **16** to form ring-closed product **17** under the conditions on Table 3, probably due to the carbonyl groups of triamides **15** and **16** don't have enough reactive.

Table 3.

Studies on construction of the D ring[a]



Entry	Substrate	Reductive agent	Lewis acid	Solvent	Temp. /°C	Result
1	**15**	LAH	-	THF	25-75	Decomposed
2	**15**	AlH_3-Me_2NEt	-	THF	0-75	Decomposed
3	**15**	$NaBH_4$	$CoCl_2$	MeOH	0-75	Decomposed
4	**16**	LAH	-	THF	25-75	Decomposed
5	**16**	AlH_3-Me_2NEt	-	THF	0-75	Decomposed
6	**16**	$NaBH_4$	$CoCl_2$	MeOH	0-75	Decomposed

[a] All reaction conditions unless otherwise specified: 0.1 mmol of **15** or **16**, 0.5-1 mmol of reductive agent, 0.12 mmol of Lewis acid, 1 mL of solvent, 12 h.

3. Conclusions

In summary, we have developed an efficient approach to construct system with two quaternary centers of the perophoramidine core skeleton via Morita-Baylis-Hillman (MBH) reaction as the key step. Further application of this process is under investigation.

4. Experimental section

4.1. General

Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or under a UV lamp. 1H and ^{13}C NMR spectra were recorded with a spectrometer operating at 400 or 600 MHz for proton and carbon nuclei, respectively. High-resolution mass spectra (HRMS) was obtained using positive electrospray ionization by the TOF method.

4.2. (R)-methyl2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl) acrylate (1)

Isatin (10 g, 68.0 mmol) was dissolved in DMF (100 mL) and cooled to 0 °C in an ice bath. Sodium hydride (60% wt, 3.3 g, 81.6 mmol) was added and the solution was stirred for 10 minutes before addition of methyl iodide (4.7 mL, 74.83 mmol). The resulting solution was stirred at this temperature for 20 minutes and quenched with water and extracted three times with EtOAc. The combined organic layers were dried over sodium sulfate and concentrated, and then red solid was obtained. To a solution of the above red solid in methyl acrylate (100 mL) was added triethylenediamine (4.4 g, 20.0 mmol). The solution was stirred for 38 h at room temperature and then washed with water, extracted with EtOAc twice and dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum and ethyl acetate (2:1) to give the titled compound **1** (14.8 g, 88%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 1H), 7.11 (d, *J* = 8 Hz, 1H), 6.99-6.96 (m, 1H), 6.81 (d, *J* = 8 Hz, 1H), 6.48 (d, *J* = 20 Hz, 2H), 4.70 (s, 1H), 3.54 (s, 3H), 3.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 165.1, 144.5, 139.2, 130.1, 129.6, 127.9, 123.7, 123.0, 108.6, 76.2, 52.0, 26.4 ppm. ESI HRMS calcd for $C_{13}H_{14}NO_4$+H 248.0923, found 248.0912.

4.3 Methyl2-((S)-3-((R)-1-cyano-2-ethoxy-2-oxoethyl)-1-methyl-2-oxoindolin-3-yl) acrylate (2)

To a solution of **1** (10 g, 40.5 mmol) and di-t-Butyl decarbonate (10.6 g, 48.6 mmol) in CH_2Cl_2 (100 mL), 4-dimethylamino pyridine (98.8 mg, 0.8 mmol) was added. The solution was stirred for 9 h at -10 °C and then washed with water, extracted with CH_2Cl_2 twice and dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum andethyl acetate (6:1) to afford a yellow solid. To a solution of the above solid in methylbenzene (100 mL), ethyl cyanacetate (4.6 mL, 42.7 mmol) and triethylenediamine (783 mg, 3.56 mmol) were added at room temperature. After 1 h, the reaction mixture was washed with water, extracted with EtOAc twice and dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum and ethyl acetate (5:1) to afford compound **2** (11.6 g, 84 %) as a light red solid. ^1H NMR (600 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.2 Hz, 1H), 7.32-7.30 (m, 1H), 7.07-7.04 (m, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H), 5.57 (s, 1H), 5.35 (s, 1H), 3.97-3.92 (m, 2H), 3.72 (s, 3H), 3.16 (s, 3H), 0.99-0.97 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 166.0, 163.2, 144.0, 136.4, 130.1, 129.1, 126.6, 124.9, 123.2, 114.8, 108.9, 62.9, 55.3, 52.5, 42.6, 26.8, 13.6 ppm. ESI HRMS calcd for $C_{18}H_{18}N_2O_5$+H 342.1216, found 343.1310.

4.4 methyl2-(3-(cyanomethyl)-1-methyl-2-oxoindolin-3-yl) acrylate (3)

A solution of **2** (9 g, 26.3 mmol) in dimethyl sulfoxide (90 mL) and water (9 mL) was heated to 125 °C for 30 h. Then the mixture was extracted with EtOAc twice, washed with water twice, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum and ethyl acetate (5:1) to afford compound **3** (6.5 g, 85 %) as a light red solid. ^1H NMR (600 MHz, $CDCl_3$): δ 7.31-7.28 (m, 1H), 7.20-7.17 (m, 1H), 7.02-7.00 (m, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.54 (s, 1H), 6.02 (s, 1H), 3.52 (s, 3H), 3.23 (s, 3H), 3.09-3.06 (m, 1H), 2.78-2.76 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 164.8, 144.0, 137.3, 129.8, 128.7, 128.2, 123.3, 123.1, 115.8, 108.9, 52.4, 51.5, 26.8, 24.8 ppm. ESI HRMS calcd for $C_{15}H_{14}N_2O_3$+H 271.1004, found 271.1011.

4.5 methyl2-(3-(cyanomethyl)-1-methyl-2-oxoindolin-3-yl) pent-4-enoate (4)

To a solution of **3** (8 g, 29.6 mmol) in dry THF (100 mL) at -78 °C under argon atmosphere, vinyl magnesium bromide solution (1 M in THF, 32.6 mL, 32.6 mmol) was added in a dropwise manner over 10 minutes. After 1.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with EtOAc twice, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum and ethyl acetate (7:1) to afford compound **4** (7.1 g, 80%) as a light yellow solid. ^1H NMR (600 MHz, $CDCl_3$): δ 7.39-7.36 (m, 1H), 7.30-7.29 (m, 1H), 7.14-7.11 (m, 1H), 6.91-6.90 (m, 1H), 5.68-5.61 (m, 1H), 4.98-4.95 (m, 2H), 3.66 (s, 3H), 3.32-3.29 (m, 1H), 3.23 (s, 3H), 2.92-2.86 (m, 1H), 2.88-2.86 (m, 1H), 2.42-2.33 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 171.5, 143.5, 134.3, 129.9, 128.0, 123.5, 123.4, 117.6, 116.2, 108.9, 51.9, 49.7, 49.5, 30.7, 26.6, 23.1 ppm. ESI HRMS calcd for $C_{17}H_{18}N_2O_3$+H 299.1317, found 299.1391.

4.6 methyl2-(3-(cyanomethyl)-1-methyl-2-oxoindolin-3-yl)-4-oxobutanoate (5)

A solution of **4** (10.0 g, 33.6 mmol) in CH_2Cl_2 (60 mL) and MeOH (40 mL) was cooled to −78 °C. Ozone was then bubbled through the solution for 1.5 h when it became yellow and the flow of ozone was stopped. To the above solution was added dimethyl sulfide (2.9 mL, 40.3 mmol) at −78 °C. After being stirred at this temperature for 15 minutes, the reaction mixture was warmed to room temperature, stirred for an additional 12 h, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with petroleum and ethyl acetate (2:1) to give **5** (8.3 g, 82%) as a yellow solid. ^1H NMR (600 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.40-7.38 (m, 1H), 7.35-7.34 (m, 1H), 7.15-7.13 (m, 1H), 6.94-6.92 (m, 1H), 3.73 (s, 3H), 3.57-3.56 (m, 1H), 3.26-3.24 (m, 4H), 2.89-2.80 (m, 2H), 2.28-2.25 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 174.5, 170.4, 143.3, 130.2, 127.7, 123.7, 123.5, 116.1, 109.2, 52.6, 49.3, 42.9, 40.7, 26.6, 24.3 ppm. ESI HRMS calcd for $C_{16}H_{16}N_2O_4$+H 301.1110, found 301.1188.

4.7 2-(1-methyl-2-oxo-3-(2-oxotetrahydrofuran-3-yl) indolin -3-yl) acetonitrile (6)

To a solution of **5** (9 g, 30.0 mmol) in MeOH (100 mL) at 0 °C was added sodium borohydride (8.0 g, 210.0 mmol) over 20 minutes. After being stirred for 5 h at room temperature, the reaction mixture was diluted with EtOAc, quenched with a saturated NH_4Cl solution in an ice bath. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with a saturated NaCl solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with petroleum and ethyl acetate (2:1) to give **6** (6.9 g, 80%) as a white solid. ^1H NMR (600 MHz, $CDCl_3$): δ 7.44-7.43 (m, 1H), 7.35-7.33 (m, 1H), 7.10-7.08 (m, 1H), 6.88-6.87 (m, 1H), 4.23-4.19 (m, 1H), 4.12-4.08 (m, 1H), 3.33-3.30 (m, 1H), 3.27-3.24 (m, 1H), 3.21 (s, 3H), 2.79-2.76 (m, 1H), 2.27-2.21 (m, 1H), 1.94-1.87 (m, 1H)

ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 174.2, 143.7, 130.1, 127.5, 123.6 (d, *J* = 14.8 Hz, 1H), 116.2, 109.2, 65.9, 48.7, 43.6, 26.7, 25.1, 24.0 ppm. ESI HRMS calcd for $C_{15}H_{14}N_2O_3$+H 271.1004, found 271.0744.

4.8 3'-(2-hydroxyethyl)-1-methylspiro[indoline-3,4'-

piperidine]-2,2'- dione (7)

To a solution of **6** (8.1 g, 30.0 mmol) and Cobaltous chloride (55% wt, 10.7 g, 45 mmol) in MeOH (100 mL) at 0 °C was added sodium borohydride (1.7 g, 45. 0 mmol) over 20 minutes. After being stirred for 10 h at 60 °C, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with CH_2Cl_2 and MeOH (20:1) to give **7** (7.3 g, 89%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36-7.33 (m, 1H), 7.21-7.19 (m, 1H), 7.15-7.12 (m, 1H), 6.89-6.88 (m, 1H), 6.22 (s, 1H), 5.03-5.01 (m, 1H), 4.01-3.96 (m, 1H), 3.63-3.58 (m, 1H), 3.38-3.30 (m, 2H), 3.23 (s, 3H), 2.80-2.78 (m, 1H), 2.33-2.27 (m, 1H), 1.92-1.85 (m, 2H), 0.94-0.91 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 174.2, 143.4, 131.3, 128.9, 123.2, 122.1, 108.4, 62.7, 50.6, 46.8, 37.9, 30.8, 29.1, 26.2 ppm. ESI HRMS calcd for $C_{15}H_{18}N_2O_3$+H 275.1317, found 275.1425.

4.91'-benzoyl-3'-(2-hydroxyethyl)-1-methylspiro[indoline-3,4'
-piperidine]-2,2'-dione (9)

To a solution of lactam **7** (8.0 g, 29.2 mmol), 4-dimethylaminopyridine (356.2 mg, 2.9 mmol) and triethylamine (5.3 mL, 38.0 mmol) in MeCN (100 mL) under nitrogen was added benzoyl chloride (1.7 g, 45.0 mmol) over 10 minutes. And the resulting mixture solution was stirred at room temperature for 1.5 h and then at 70 °C overnight. After completion of the reaction, water (30 mL) was added in one portion and the reaction mixture was stirred at 70 °C for 1 h to hydrolyze excess Bz_2O. The residue mixture was cooled to temperature, and then diluted with saturated $NaHCO_3$, extracted with EtOAc twice, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum/ethyl acetate (1:2) to afford compound **9** (7.2 g, 65%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.90 (m, 2H), 7.57-7.54 (m, 1H), 7.48-7.41 (m, 2H), 7.29-7.25 (m, 1H), 7.08-7.07 (m, 1H), 6.88-6.85 (m, 2H), 5.97 (s, 1H), 4.42-4.36 (m, 1H), 4.34-4.29 (m, 1H), 3.99-3.92 (m, 1H), 3.36-3.34 (m, 1H), 3.23 (s, 3H), 2.88 (s, 1H), 2.34-2.26 (m, 1H), 2.22-2.14 (m, 1H), 1.89 (d, J = 12 Hz, 1H), 1.19-1.15 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 172.7, 166.1, 143.2, 132.8, 131.5, 130.4, 129.6, 128.7, 128.2, 123.0, 122.2, 108.4, 64.6, 50.3, 42.6, 37.9, 31.4, 26.4, 26.2 ppm. ESI HRMS calcd for $C_{22}H_{22}N_2O_4$+H 379.1580, found 379.1666.

4.102-(1'-benzoyl-1-methyl-2,2'-dioxospiro[indoline-3,4'-piper
idin] -3'-yl)ethyl benzoate (9′)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 5.2 Hz, 2H), 7.77 (d, *J* = 5.2 Hz, 2H), 7.59-7.57 (m, 1H), 7.51-7.49 (m, 1H), 7.46-7.42 (m, 4H), 7.33-7.30 (m, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 6.95-6.93 (m, 1H), 6.89 (d, *J* = 5.2 Hz, 1H), 4.42-4.37 (m, 1H), 4.25-4.21 (m, 2H), 3.94-3.90 (m, 1H), 3.25 (s, 3H), 3.13 (d, *J* = 6 Hz, 1H), 2.43-2.38 (m, 1H), 2.26-2.22 (m, 1H), 2.13-2.08 (m, 1H), 1.11-1.06 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 173.5, 173.2, 166.1, 143.4, 135.8, 132.9, 131.6, 131.4, 130.1, 129.5, 129.0, 128.3, 128.2, 128.1, 123.2, 122.1, 108.6, 63.7, 50.9, 45.5, 40.9, 32.4, 26.3, 25.2 ppm. ESI HRMS calcd for $C_{25}H_{26}N_2O_4$+H 483.1920, found 483.1932.

4.10 3'-allyl-1'-benzoyl-3'-(2-hydroxyethyl)-1-methylspiro
[indoline-3,4'-piperidine]-2,2'-dione (10)

To a solution of **9** (3.0 g, 7.8 mmol), Potassium tert-butoxidein (1.4 g, 12.0 mmol) and 18-Crown-6 (1.1 g, 4.0 mmol) in THF (40 mL) at 50 °C was added allyl bromide (1.0 mL, 11.7 mmol) in a dropwise manner over 5 minutes. The reaction mixture was stirred overnight and extracted with EtOAc twice, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum and ethyl acetate (1:1) to afford compound **10** (1.8 g, 55 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H), 7.55-7.51 (m, 1H), 7.45-7.41 (m, 2H), 7.36-7.33 (m, 1H), 7.10-7.06 (m, 2H), 6.93-6.91 (m, 1H), 5.97-5.87 (m, 1H), 5.31-5.28 (m, 2H), 4.38-4.36 (m, 2H), 4.25-4.20 (m, 1H), 4.12-4.06 (m, 1H), 3.56-3.52 (m, 2H), 3.25 (s, 3H), 3.17-3.15 (m, 1H), 2.50-2.42 (m, 1H), 2.00-1.92 (m, 1H), 1.75-1.71 (m, 1H), 1.09-1.02 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 170.5, 166.4, 143.5, 132.7, 132.3, 129.7, 128.9, 128.8, 128.2, 124.1, 122.9, 118.6, 108.7, 64.2, 51.0, 49.8, 43.5, 42.5, 31.2, 27.5, 26.5 ppm. ESI HRMS calcd for $C_{25}H_{26}N_2O_4$+H 419.1893, found 419.1981.

4.123'-(2-(allyloxy)ethyl)-1'-benzoyl-1-methylspiro[indoline-3,
4'-piperidine]-2,2'-dione (10′)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 2H), 7.57-7.53 (m, 1H), 7.44-7.40 (m, 2H), 7.28-7.24 (m, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.86-6.82 (m, 2H), 5.94-5.84 (m, 1H), 5.35-5.31 (m, 1H), 5.25-5.23 (m, 1H), 4.46-4.41 (m, 1H), 4.38-4.33 (m, 1H), 4.20-4.15 (m, 1H), 4.08-4.03 (m, 1H), 3.93-3.86 (m, 1H), 3.30-3.22 (m, 4H), 2.92-2.91 (m, 1H), 2.35-2.28 (m, 1H), 2.21-2.13 (m, 1H), 1.91-1.88 (m, 1H), 1.18-1.11 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 170.2, 166.0, 143.1, 132.7, 132.6, 131.5, 129.5, 128.6, 128.1, 122.9, 122.1, 117.3, 108.3, 64.7, 50.6, 50.0, 43.0, 42.7, 31.3, 27.0, 26.1 ppm. ESI HRMS calcd for $C_{25}H_{26}N_2O_4$+H 419.1871, found 419.1906.

4.112-(1'-benzoyl-3'-(2-hydroxyethyl)-1-methyl-2,2'-dioxospir
o[indoline-3,4'-piperidine]-3'-yl) acetaldehyde (11)

A solution of **10** (1.26 g, 3 mmol) in CH_2Cl_2 (15 mL) and MeOH (10 ml) was cooled to −78 °C. Ozone was then bubbled through the solution for 0.5 h, when the mixture became yellow and the flow of ozone was stopped. To the above solution was added dimethyl sulfide (0.3 mL, 4.1 mmol) at −78 °C. After being stirred at this temperature for 10 minutes, the reaction mixture was warmed to room temperature, stirred for an additional 12 h, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with petroleum and ethyl acetate (2:1) to give **11** (1.0 g, 82%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.06-8.04 (m, 2H), 7.68-7.67 (m, 1H), 7.54-7.52 (m, 1H), 7.44-7.42 (m, 2H), 7.38-7.36 (m, 1H), 7.19-7.17 (m, 1H), 6.94-6.92 (m, 1H), 4.81-4.78 (m, 1H), 4.34-4.32 (m, 2H), 3.98-3.95 (m, 1H), 3.79-3.76 (m, 1H), 3.51-3.50 (m, 1H), 3.26-3.21 (m, 4H), 2.56-2.51 (m, 1H), 1.98-1.93 (m, 1H), 1.79-1.77 (m, 1H), 1.10-1.05 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 177.6, 171.6, 166.4, 143.4, 132.7, 130.4, 129.7, 128.9, 128.5, 128.3, 124.9, 123.3, 108.6, 64.0, 57.9, 51.3, 46.0, 42.0, 31.2, 27.5, 26.6 ppm. ESI HRMS calcd for $C_{24}H_{24}N_2O_5$+H 421.1719, found 421.1696.

4.12methyl2-(1'-benzoyl-3'-(2-hydroxyethyl)-1-methyl-2,2'-di
oxospiro[indoline-3,4'-piperidin]-3'-yl) acetate (14)

To a solution of **11** (0.8 g, 1.9 mmol) in MeOH (25 mL) was added N-Iodosuccinimide (1.1 g, 4.8 mmol) and K_2CO_3 (662 mg, 4.8 mmol). The reaction mixture was stirred at room temperature

for 2.5 h, at which TLC analysis indicated complete consumption of starting material. The saturated $Na_2S_2O_3$ solution was added to destroy any remaining N-Iodosuccinimide or hypoiodite species. The resultant mixture was extracted with EtOAc twice, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum and ethyl acetate (1:1) to afford compound **14** (684 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (m, 2H), 7.73-7.71 (m, 1H), 7.54-7.50 (m, 1H), 7.44-7.40 (m, 2H), 7.37-7.33 (m, 1H), 7.18-7.14 (m, 1H), 6.93-6.91 (m, 1H), 4.75-4.70 (m, 1H), 4.36-4.32 (m, 2H), 3.89-3.85 (m, 1H), 3.82 (s, 3H), 3.77-3.73 (m, 1H), 3.53-3.51 (m, 1H), 3.25 (s, 3H), 3.22-3.19 (m, 1H), 2.73-2.71 (m, 1H), 2.55-2.49 (m, 1H), 2.00-1.93 (m, 1H), 1.78-1.75 (m, 1H), 1.10-1.04 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 171.7, 169.7, 166.4, 143.3, 132.7, 130.5, 129.7, 128.8, 128.6, 128.2, 125.0, 123.3, 108.6, 64.1, 52.3, 51.4, 49.3, 45.9, 42.1, 31.1, 29.6, 27.5, 26.5 ppm. ESI HRMS calcd for $C_{25}H_{26}N_2O_6$+H 451.1824, found 451.1915.

4.132-(3'-(2-hydroxyethyl)-1-methyl-2,2'-dioxospiro[indoline-3,4'-piperidin]-3'-yl)-N-methylacetamide (15)

To a solution of **14** (135 mg, 0.3 mmol) in 5 mL MeOH was added $MeNH_2$ (2.5 mL, 30% in MeOH) at room temperature, and the mixture was then stirred overnight. After evaporation, the residue was directly applied to silica gel column chromatography eluting with CH_2Cl_2 and MeOH (20:1) to afford compound **15** (72.4 mg, 70%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.50 (m, 1H), 7.30-7.27 (m, 1H), 7.11-7.07 (m, 2H), 6.88-6.86 (m, 1H), 4.64 (s, 1H), 4.24-4.21 (m, 1H), 3.95-3.91 (m, 1H), 3.83-3.67 (m, 2H), 3.56-3.46 (m, 3H), 3.19 (s, 3H), 2.98-2.96 (m, 1H), 2.78-2.77 (m, 3H), 2.38-3.31 (m, 1H), 1.79-1.74 (m, 2H), 1.65-1.56 (m, 1H), 0.94-0.94 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 172.9, 168.8, 143.1, 128.9, 128.4, 124.9, 123.4, 108.6, 67.9, 61.8, 51.5, 46.2, 45.3, 30.9, 30.0, 26.5, 26.2, 25.6 ppm. ESI HRMS calcd for $C_{18}H_{23}N_3O_4$+H 346.1722, found 346.1706.

4.142-(1'-benzoyl-3'-(2-hydroxyethyl)-1-methyl-2,2'-dioxospiro[indoline-3,4'-piperidin]-3'-yl) acetamide (16)

To a solution of **14** (100 mg, 0.22 mmol) in 5 mL MeOH was added $NH_3{\cdot}H_2O$ (2 mL, 35% in H_2O) at room temperature, and the mixture was then stirred for 1.5 h. After evaporation, the residue was directly applied to silica gel column chromatography eluting with CH_2Cl_2 and MeOH (20:1) to afford compound **16** (72 mg, 75%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04-8.03 (m, 2H), 7.55-7.52 (m, 1H), 7.50-7.48 (m, 1H), 7.44-7.41 (m, 2H), 7.36-7.34 (m, 1H), 7.14-7.11 (m, 1H), 6.93-6.92 (m, 1H), 6.50 (s, 1H), 5.57 (s, 1H), 4.37-4.29 (m, 3H), 3.98-3.96 (m, 1H), 3.86-3.82 (m, 1H), 3.65-3.61 (m, 1H), 3.25 (s, 3H), 3.15-3.13 (m, 1H), 2.48-2.43 (m, 1H), 1.98-1.93 (m, 1H), 1.86-1.82 (m, 1H), 1.22-1.16 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 175.1, 171.8, 170.8, 166.4, 143.2, 132.7, 130.3, 129.6, 128.9, 128.4, 128.2, 124.8, 123.2, 108.6, 64.0, 51.4, 51.1, 46.2, 42.4, 30.5, 27.6, 26.5ppm. ESI HRMS calcd for $C_{24}H_{25}N_3O_5$+H 436.1828, found 436.1831.

Acknowledgements

We are grateful for the financial support from the NSFC (2102106, 21572138).

Supplementary data

Supplementary data associated with this article can be found in the online version.

References and notes

1. (a) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124–7126; (b) Verotta, L.; Pilati, T.; Tato, M.; Elisabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Nat. Prod*. **1998**, *61*, 392–396.
2. (a) Denault, J. B.; Salvesen, G. S. *Chem. Rev*. **2002**, *102*, 4489–4500; (b) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod*. **2004**, *67*, 78–81; (c) Denault, J. B.; Salvesen, G. S. *Chem. Rev*. **2002**, *102*, 4489−4499.
3. Fuchs, R.; Funk, R. L. *J. Am. Chem. Soc*. **2004**, *126*, 5068–5069.
4. Novikov, A. J.; Rainier, D. *Angew. Chem. Int. Ed*. **2006**, *45*, 4317–4320.
5. Wu, H.; Xiao, F. X.; Qin, Y. *J. Am. Chem. Soc*. **2010**, *132*, 14052–14054.
6. Zhang, H.; Hong, L.; Kang, H.; Wang, R. *J. Am. Chem. Soc*. **2013**, *135*, 14098– 14101.
7. Trost, B. M.; Kruger, M. S.; Zhang, Y. *Chem. Sci*. **2015**, *6*, 349–353.
8. (a) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett*. **2006**, *8*, 2187–2190; (b) Seo, J. H.; Artman, G. D.; Weinreb, S. M. *J. Org. Chem*. 2006, **71**, 8891–8900; (c) Schammel, A. W.; Chiou, G.; Garg, N. K.; *Org. Lett.* **2012**, *17*, 4556–4559; (d) Ishiji, T.; Takemoto, Y. *Tetrahedron* **2013**, *69*, 4517–4523; (e) Ishida, T.; Ikota, H.; Kurahashi, K.; Tsukano, C.; Takemoto, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 10204–10207; (f) Trost, B. M.; Osipov, M. *Chem. Eur. J*. **2015**, *21*, 16318–16343; (g) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem.* **2006**, *118*, 4423–4426; (h) Ishida, T.; Ikota, H.; Kurahashi, K.; Tsukano, C.; Takemoto, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 10204–10207; (i) Morales-Rios, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron* **1996**, *52*, 5339–5348; (j) Evans, M. A.; Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2009**, *65*, 6712–6719; (k) Han, S. J.; Vogt, F.; Krishnan, S.; May, J. A.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 3316–3319; (l) Han, S. J.; Vogt, F.; May, J. A.; Krishnan, S.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *J. Org. Chem*. **2015**, *80*, 528–547; (m) Wilkie, R. P.; Neal, A. R.; Johnston, C. A.; Voute, N.; Lancefield, C. S.; Stell, M. D.; Medda, F.; Makiyi, E. F.; Turner, E. M.; Ojo, O. S.; Slawin, A. M. Z.; Lebl, T.; Mullen, P.; Harrison, D. J.; Irelandc, C. M.; Westwood, N. J. *Chem. Commun*. **2016**, *52*, 10747–10750; (n) Popov, K.; Hoang, A.; Somfai, P. *Angew .Chem. Int. Ed*. **2016**, *55*,1801–1804; (o) Artman, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523–1526; (p) Hoang, A.; Popov, K.; Somfai, P. *J. Org. Chem.* **2017**, *82*, 2171–2176; (q) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447–457; (r) Du, Y.; Wu, H.; Song, H.; Qin, Y.; Zhang, D. *Chin. J. Chem*. **2012**, *30*, 2970–1973.
9. (a) Gardena, S. J.; Skakle, J. M. S. *Tetrahedron Lett.* **2002**, *43*, 1969–1972; (b) Qian, J. Y.; Wang, C. C.; Sha, F.; Wu, X. Y.; *RSC Adv*. **2012**, *2*, 6042–6048; (c) Shanmugam, P.; Vaithiyanathan, V. *Can. J. Chem*. **2009**, *87*, 591–599; (d) Liu, X. W.; Han, W. Y.; Liu, X. L.; Zhou, Y.; Zang, X. M.; Yuan, W. Chen. *Tetrahedron* **2014**, *70*, 9191–9197; (e) Chen, G. Y.; Zhong, F.; Lu, Y. *Org. Lett.* **2012**, *14*, 3955–3957; (f) Liu, X. L.; Yuan, W. C.; Huang, W. C.; Zhou, Y.; Feng, T. T.; Lin, B. *CN 103936649 B*; (g) Wang, C. C.; Wu, X. Y. *Tetrahedron* **2011**, 67, 2974–2978; (i) Yun, M. J.; Yang, J. I.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002,** 23, 1651–1654; (j) Fan, X.; Yang, H. B.; Shi, M. *Adv. Synth. Catal*. **2017**, 359, 49-57; (k) Dong, Z.; Yan, C.; Gao, Y. Z.; Dong, C, Qiu, G. F.; Zhou, H. B. *Adv. Synth. Catal.* **2015**, 357, 2132–2142; (l) Malini, K.; Periyaraja, S.; Shanmugam, P. *Tetrahedron Lett.* **2015**, 56, 5123–5127; (m) Nezhad, A. K.; Mohammadi, S. *Synthesis*. **2012**, 44, 1725–1735.

10. Crystallographic Data for **7**: CCDC 1532495, $C_{15}H_{18}N_2O_3$, M:274.31, Space group: P -1, Cell: a = 7.8109(7), b = 8.1431(9), c = 12.2697(13), alpha = 102.257(9), beta = 99.744(8), gamma = 111.689(9), Temperature: 293K, calcd: 1.336 g/cm^{-3}.
11. For more details, see the Supporting Information.
12. Liu, X. L.; Zhang, W. H.; Yao, Zh.; Liu, X. W.; Peng, L. J.; Zhao, Z.; Lu, Y.; Zhou, Y.; Yuan, W. C. *Tetrahedron* **2015**, *71*, 9483–9495.