



Pd(II)-catalyzed annulation of *N*-benzyl-*N*-aroylmethyl-2-alkynamides with arylboronic acids: an efficient synthesis of highly substituted α -alkylidene- β -hydroxy- γ -lactams

Huan Wang, Xiuling Han*, Xiyan Lu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

ARTICLE INFO

Article history:

Received 15 August 2010
Received in revised form 27 September 2010
Accepted 29 September 2010
Available online 16 October 2010

Keywords:

Palladium(II)
Ketone
Arylboronic acid
Lactam
Carbopalladation

ABSTRACT

A simple palladium(II)-catalyzed intramolecular addition of vinylpalladium species to ketones initiated by the carbopalladation of alkynamides under mild conditions without a Pd(II)/Pd(0) redox system was developed. This cascade reaction provides a new approach for the synthesis of highly substituted α -alkylidene- β -hydroxy- γ -lactams.

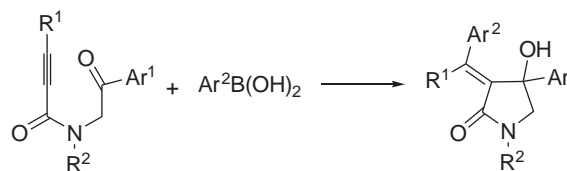
© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Biologically active substances possessing lactam units are found common in natural sources.^{1,2} According to some recent researches, the γ -lactam skeleton shows cytotoxicity, antitumor, and antiinflammation activities and are less toxic compared to the corresponding lactones.³ Especially highly substituted lactams possess different biological activities.⁴ In addition, the γ -lactam functionality is a prevalent theme in various natural product synthesis and serves as a crucial intermediate for numerous natural products.⁵ Although different methods have been developed to construct this kind of structures,⁶ much more attention can never be enough. As a potential precursor for synthesis of natural products, α -alkylidene- γ -lactams attracted our interest. In earlier work, our group has constructed this kind of unit in different ways.^{6a–q}

The addition of specific carbon nucleophiles to carbon-heteroatom multiple bond, such as C=O,⁷ C=N,⁸ CN⁹ is an attractive synthetic methodology for forming C–C bonds. Compared to Rh species, organopalladium(II) species are more electrophilic and can easily react with some nucleophiles, such as carbon, oxygen or nitrogen anions. Although a few papers have reported the nucleophilic reactions,^{7c,d,9b} most of these reactions were catalyzed by Pd(0) species, and involved a Pd(II)/Pd(0) redox system. Thus, it is a challenge to accomplish a nucleophilic addition reaction for Pd(II) species.

Recently, we reported some Pd(II)-catalyzed addition reactions to carbon-heteroatom multiple bonds^{10,11a–c} initiated by carbopalladation of alkynes with arylboronic acids.¹¹ In all of these reactions, palladium(II) complexes were used as catalysts and no redox system was required. Inspired by these works, we wonder if we can construct the α -alkylidene- γ -lactam unit in one-step through the similar route (Scheme 1). Recently, Corey reported the total synthesis of Salinosporamide A and its analogues with the similar α -methylene- β -hydroxy- γ -butyrolactam structure as the intermediate.⁵



Scheme 1. The proposed reaction.

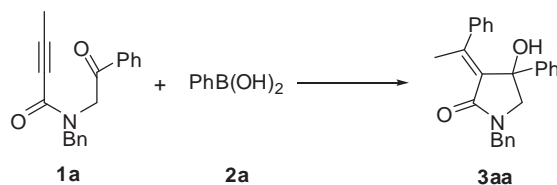
2. Results and discussion

To begin the study of the annulation reaction, the effect of different catalysts was first surveyed using *N*-benzyl-*N*-benzoylmethyl-but-2-ynamide (**1a**) as the substrate. It was found that the reaction did work when using some neutral or cationic Pd(II)/dppp (or bpy) species to give α -alkylidene- β -hydroxy- γ -butyrolactams as the product. Cationic palladium species and Pd(CF₃COO)₂ can only

* Corresponding authors. Tel.: +86 21 54925158; fax: +86 21 64166128; e-mail address: xylu@mail.sioc.ac.cn (X. Lu).

give moderate yields of the product in dioxane (or DCE) and H₂O (Table 1, entries 1–8) at 80 °C or elevated temperature. Pd(OAc)₂/bpy can provide the product in good yield (Table 1, entry 9). The reaction did not occur in the absence of the ligand (Table 1, entry 10).

Table 1
Screening of catalysts^a



Entry	Catalyst	Solvent (v/v)	Temperature (°C)	Time (h)	Yield ^b (%)
1 ^c	[dpppPd(H ₂ O) ₂] ²⁺ (BF ₄) ₂	Dioxane/H ₂ O (10/1)	80	14	48
2 ^c	[dpppPd(H ₂ O) ₂] ²⁺ (OTf ⁻) ₂	Dioxane/H ₂ O (10/1)	80	14	41
3 ^c	[dpppPd(H ₂ O) ₂] ²⁺ (OTf ⁻) ₂	Dioxane/H ₂ O (10/1)	Reflux	8	52
4	[dpppPd(H ₂ O) ₂] ²⁺ (OTf ⁻) ₂	DCE/H ₂ O (20/1)	80	40	42
5	[bpyPd(H ₂ O) ₂] ²⁺ (OTf ⁻) ₂	DCE/H ₂ O (20/1)	80	8	52
6 ^d	Pd (CF ₃ COO) ₂ /dppp	DCE/H ₂ O (20/1)	80	48	39
7 ^d	Pd (CF ₃ COO) ₂ /bpy	DCE/H ₂ O (20/1)	80	40	75
8 ^d	Pd(CF ₃ COO) ₂ /NO ₂ -bpy	DCE/H ₂ O (20/1)	80	72	57
9 ^d	Pd (OAc) ₂ /bpy	DCE/H ₂ O (20/1)	Reflux	2	88
10 ^d	Pd (OAc) ₂	DCE/H ₂ O (20/1)	Reflux	72	—

^a Reaction conditions: **1a** (0.1 mmol), phenylboronic acid (1.3 equiv), catalyst (5 mol %), solvent/H₂O (2 mL/0.1 mL).

^b Isolated yield.

^c Solvent/H₂O (1 mL/0.1 mL).

^d Catalyst (5 mol %)/ligand (6 mol %).

Then the effect of solvent to the reaction was studied as shown in Table 2. It was found that the reaction can proceed smoothly in DCE or benzene at reflux, giving the product in excellent yields in 3 h or 16 h, respectively (Table 2, entries 4 and 8). The water also has some influence to the reaction. The reaction gave a lower yield of the product in the absence of water (Table 2, entry 9). Finally, DCE was chosen as the best solvent in consideration of its shorter reaction time. The effect of temperature on the reaction was investigated (Table 2, entries 10–13). The reaction gave the best yield at reflux, and lower temperature made the reaction time longer and yield lower.

Table 2
Screening of solvents and temperature^a

Entry	Solvent	Temperature (°C)	Time (h)	Yield ^b (%)
1	Dioxane	80	60	5
2	Toluene	80	60	64
3	CHCl ₃	Reflux	60	46
4	DCE	Reflux	3	87
5	THF	Reflux	72	20
6	CH ₃ CN	Reflux	15	73
7	CH ₂ Cl ₂	Reflux	3	77
8	Benzene	Reflux	16	88
9 ^c	DCE	Reflux	4	76
10	DCE	90	2	87
11	DCE	80	2	75
12	DCE	68	7	79
13	DCE	rt	48	62

^a Reaction conditions: **1a** (0.1 mmol), phenylboronic acid (1.3 equiv), Pd(OAc)₂ (5 mol %)/bpy (6 mol %), solvent/H₂O (2 mL/0.1 mL).

^b Isolated yield.

^c Reaction in DCE in the absence of water.

On the basis of the above screening procedure, the optimal condition for this tandem annulation reaction was as follows: substrate (0.1 mmol), phenylboronic acid (1.3 equiv), Pd(OAc)₂ (5 mol %), bpy (6 mol %), DCE (2 mL), H₂O (0.1 mL) at reflux.

With the effective catalytic system in hand, the application scope of this reaction with various substituted ynamides and

arylboronic acids was explored. As shown in Table 3, this reaction proceeded well with various substrates, and some different kinds of electronically and sterically diverse functional groups can be tolerated. Substrates with methyl, *n*-propyl, TMS at the end of the

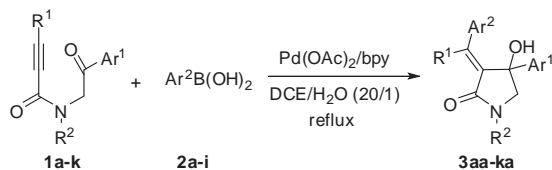
triple bond all can give corresponding products in moderate to excellent yields (Table 3, entries 1, 2, and 18). It is worth noting that the substrate **1k** with the terminal triple bond can also give the expected product in excellent yield (Table 3, entry 19). The reaction did not occur for phenyl substituted alkynamides (Table 3, entry 3). Changing the substituent on the nitrogen atom from methyl to ethyl or benzyl made no difference in reactivity, and they all proceeded with good yields (Table 3, entries 1, 4, and 5). For substrate with 4-tolyl group on the nitrogen atom, the reaction did not occur (Table 3, entry 6). Different arylboronic acids with various substituents, such as F, Cl, NO₂, OMe, etc., all proceeded well with substrate **1a** (Table 3, entries 10–17).

The stereochemistry of the exocyclic double bond in all the products was assigned as (*E*)-configuration on the basis of the lower field chemical shift of the methyl group resulting from the deshielding effect of the same side carbonyl group in ¹H NMR spectra and compared with the data in the literatures.¹² In addition, the stereochemistry of product **3aa** was confirmed by X-ray crystallography.¹³

To study further the utility of the reaction, the substrate dimethyl 2-(but-2'-ynyl)-2-benzoylmethylmalonate (**11**) was subjected to the optimal reaction condition. It can also give the expected product **31a** in 49% yield. A moderate yield (66%) could be obtained when the reaction was carried out in the presence of KF (Scheme 2).

Subsequently the possible mechanism is proposed for the reaction: first, bpyPd(OAc)₂ is formed in situ from Pd(OAc)₂ and bpy, followed by transmetalation with arylboronic acids **2** to produce the arylpalladium species **A**. Then intermediate **B** may be formed by the coordination of arylpalladium species with the triple bond and the carbonyl group of substrate **1**. The insertion of the triple bond to arylpalladium species in **B** affords vinylpalladium intermediate **C**. 1,2-Addition of the vinylpalladium species to the carbonyl group in **C** generates **D**, and finally the product **3** is formed by protonolysis of the palladium alkoxide intermediate **D** with the regeneration of the palladium(II) species to complete the catalytic cycle (Scheme 3).

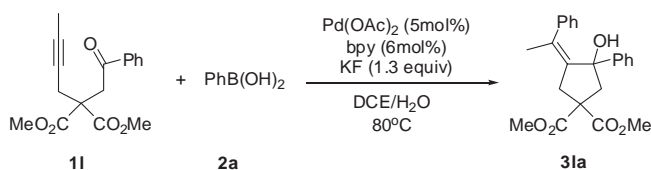
Table 3
Synthesis of substituted α -alkylidene- β -hydroxy- γ -lactams^a



Entry	1				Ar ²	Time (h)	3	Yield ^b (%)
	R ¹	R ²	Ar ¹	1				
1	Me	Bn	Ph	1a	Ph (2a)	2	3aa	88
2	ⁿ Pr	Bn	Ph	1b	Ph (2a)	0.5	3ba	91
3	Ph	Bn	Ph	1c	Ph (2a)	48	3ca	N.R.
4	Me	Me	Ph	1d	Ph (2a)	2	3da	77
5	Me	Et	Ph	1e	Ph (2a)	1.25	3ea	90
6	Me	4-Me-C ₆ H ₄	Ph	1f	Ph (2a)	48	3fa	N.R.
7	Me	Bn	4-Cl-C ₆ H ₄	1g	Ph (2a)	1.5	3ga	79
8	Me	Bn	4-Br-C ₆ H ₄	1h	Ph (2a)	2	3ha	89
9	Me	Bn	4-MeO-C ₆ H ₄	1i	Ph (2a)	0.5	3ia	88
10	Me	Bn	Ph	1a	4-Me-C ₆ H ₄ (2b)	2	3ab	92
11	Me	Bn	Ph	1a	3-Me-C ₆ H ₄ (2c)	2	3ac	78
12	Me	Bn	Ph	1a	4-MeO-C ₆ H ₄ (2d)	2	3ad	100
13	Me	Bn	Ph	1a	4-F-C ₆ H ₄ (2e)	8	3ae	77
14	Me	Bn	Ph	1a	4-Cl-C ₆ H ₄ (2f)	5	3af	73
15	Me	Bn	Ph	1a	4-Ph-C ₆ H ₄ (2g)	4	3ag	94
16	Me	Bn	Ph	1a	3-NO ₂ -C ₆ H ₄ (2h)	4	3ah	87
17	Me	Bn	Ph	1a	2-Naphthyl (2i)	4	3ai	58
18	TMS	Bn	Ph	1j	Ph (2a)	2	3ja	85
19	H	Bn	4-Cl-C ₆ H ₄	1k	Ph (2a)	1	3ka	100

^a Reaction conditions: substrate **1** (0.1 mmol), arylboronic acid (1.3 equiv), Pd(OAc)₂ (5 mol %)/bpy (6 mol %), DCE/H₂O (2 mL/0.1 mL), reflux.

^b Isolated yield.



Scheme 2. Reaction of **11**.

3. Conclusion

In conclusion, we have demonstrated an efficient approach to synthesize the highly substituted α -alkylidene- β -hydroxy- γ -lactams using Pd(OAc)₂/bpy as the catalyst. This is a tandem reaction involving carbopalladation of alkyne/1,2-addition to carbonyl groups. The asymmetric version of this cascade cyclization reaction is in progress in our group.

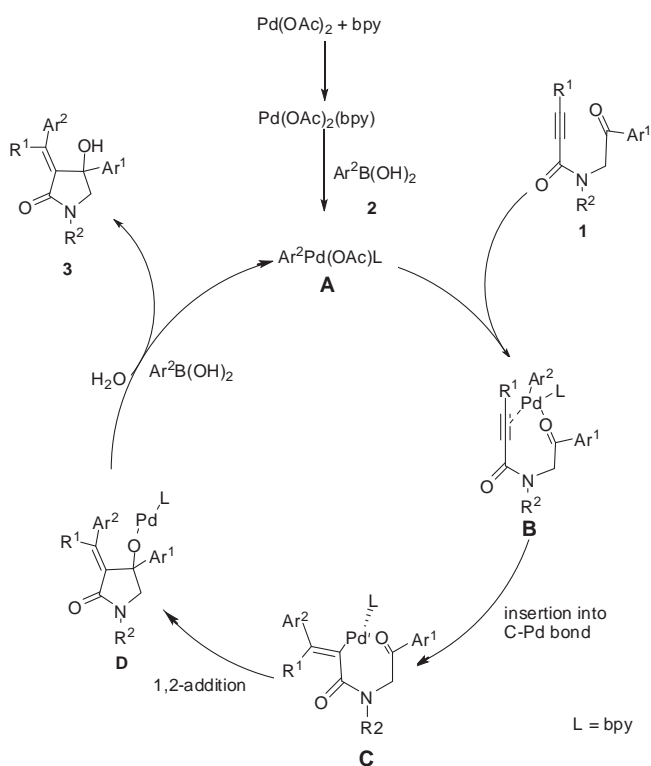
4. Experimental section

4.1. General methods

NMR spectra were recorded on a Varian Mercury V \times 300 or V \times 400 spectrometers. Infrared spectra were obtained on a Bio-Rad FTS-185 machine. Mass spectra were provided on Agilent 5973 or Agilent 1100 instruments. Elemental analyses were carried out on Elementar Vario EL instruments. Palladium acetate was purchased from Aldrich. 2,2-Bipyridine was purchased from Sinopharm Chemical Reagent Co., LtdS. All solvents were dried and distilled before use according to the standard methods. All melting points were uncorrected. BEP (2-bromo-1-ethyl-pyridinium tetrafluoroborate),¹⁴ substituted ω -bromoacetophenone,¹⁵ ω -(*N*-substituted amino)-acetophenone hydrochloride,¹⁶ 1-phenyl-2-(*p*-tolylamino)ethanone,¹⁷ but-2-ynoic acid,¹⁸ 1-bromobut-2-yne,¹⁹ dimethyl 2-(but-2-ynyl)malonate²⁰ were synthesized employing the literature procedures.

4.2. General procedure for the synthesis of *N*-benzyl-*N*-arylmethyl-2-alkynamides (**1**)^{14a}

DIEA (*N,N*-diisopropylethylamine, 3.2 equiv) was added at -10°C to a cooled mixture of ω -(*N*-substituted amino)acetophenone hydrochloride (1.1 equiv), alkynoic acid (1 mmol), BEP (1.5 equiv) in CH₂Cl₂ (10 mL) under N₂ atmosphere. The mixture was stirred at -10°C for 10 min and then reacted at room temperature until the consumption of alkynoic acid as monitored by



Scheme 3. Proposed mechanism.

TLC. Then the reaction mixture was concentrated and purified by flash chromatography on silica gel to afford the desired product.

For the characterization data of product **1a–k**, please see [Supplementary data](#).

4.3. General procedure for the synthesis of α -alkylidene- β -hydroxy- γ -lactams

Pd(OAc)₂ (5 mol %), bpy (6 mol %), and DCE (2 mL) was added into a Schlenk tube, then the mixture was stirred at reflux for 10 min. The substrate (0.1 mmol), arylboronic acid (1.3 equiv), and H₂O (0.1 mL) were added subsequently, then the mixture was reacted at reflux until the consumption of substrate as monitored by TLC. Then the reaction mixture was concentrated and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as the eluent to afford the desired product.

4.3.1. Compound 3aa. Solid; mp 158–160 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.29–7.22 (m, 5H), 7.15–7.06 (m, 8H), 6.73 (d, *J*=6.8 Hz, 2H), 4.64 (d, *J*=14.8 Hz, 1H), 4.57 (d, *J*=14.8 Hz, 1H), 3.45 (d, *J*=10 Hz, 1H), 3.27 (d, *J*=10 Hz, 1H), 2.66 (s, 3H), 2.18 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.7, 150.1, 147.3, 141.3, 136.0, 134.4, 128.7, 128.2, 128.0, 127.6, 127.5, 126.9, 126.6, 124.4, 76.4, 61.0, 46.6, 21.8; IR (KBr): ν 3285, 3062, 2915, 1659, 1492, 1431, 757, 694 cm⁻¹; MS (*m/z*, EI): 369 (M⁺), 354, 292, 278, 91 (100); calcd for C₂₅H₂₃NO₂: C, 81.27%; H, 6.27%; N, 3.79%; found: C, 81.27%; H, 6.28%; N, 3.62%.

4.3.2. Compound 3ba. Solid; mp 154–155 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.29–7.20 (m, 5H), 7.16–7.04 (m, 8H), 6.70 (d, *J*=7.2 Hz, 2H), 4.64 (d, *J*=14.4 Hz, 1H), 4.54 (d, *J*=14.4 Hz, 1H), 3.44 (d, *J*=10 Hz, 1H), 3.45–3.38 (m, 1H), 3.24 (d, *J*=10 Hz, 1H), 2.91–2.89 (m, 1H), 2.08 (s, 1H), 1.45–1.39 (m, 2H), 0.97 (t, *J*=6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 167.4, 154.4, 147.7, 139.8, 136.0, 134.5, 128.6, 128.1, 128.0, 127.5, 127.4, 127.2, 126.9, 124.3, 76.3, 60.9, 46.5, 35.7, 21.3, 14.0; IR (KBr): ν 3391, 3026, 2956, 2871, 1656, 1632, 1486, 1438, 758, 695 cm⁻¹; MS (*m/z*, EI): 397 (M⁺), 380, 354, 278, 91 (100); calcd for C₂₇H₂₇NO₂: C, 81.58%; H, 6.85%; N, 3.52%; found: C, 81.40%; H, 6.88%; N, 3.45%.

4.3.3. Compound 3da. Solid; mp 180–182 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.16–7.06 (m, 8H), 6.73 (d, *J*=6.8 Hz, 2H), 3.57 (d, *J*=10 Hz, 1H), 3.41 (d, *J*=10.4 Hz, 1H), 2.97 (s, 3H), 2.61 (s, 3H), 2.17 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.0, 149.7, 147.1, 141.4, 134.3, 128.1, 128.0, 127.3, 126.8, 126.7, 124.5, 76.1, 64.0, 29.8, 21.6; IR (KBr): ν 3300, 3059, 3022, 2937, 1670, 1658, 1492, 1450, 1281, 1213, 756, 693 cm⁻¹; MS (*m/z*, EI): 293 (M⁺), 278, 250, 207, 105 (100); calcd for C₁₉H₁₉NO₂: C, 77.49%; H, 6.53%; N, 4.77%; found: C, 77.61%; H, 6.49%; N, 4.68%.

4.3.4. Compound 3ea. Solid; mp 129–130 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.16–7.10 (m, 8H), 6.72 (d, *J*=8.8 Hz, 2H), 3.56 (d, *J*=13.2 Hz, 1H), 3.60–3.38 (m, 2H), 3.39 (d, *J*=13.6 Hz, 1H), 2.60 (s, 3H), 2.34 (s, 1H), 1.13 (t, *J*=8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 167.5, 149.5, 147.4, 141.3, 134.7, 128.1, 128.2, 128.0, 127.4, 126.8, 126.6, 124.3, 76.3, 61.1, 37.2, 21.6, 12.2; IR (KBr): ν 3367, 3025, 2978, 2938, 1658, 1631, 1601, 1485, 1448, 1431, 1283, 758, 700 cm⁻¹; MS (*m/z*, EI): 307 (M⁺), 292, 222, 207, 105, 58 (100); calcd for C₂₀H₂₁NO₂: C, 78.15%; H, 6.89%; N, 4.56%; found: C, 78.10%; H, 6.82%; N, 4.57%.

4.3.5. Compound 3ga. Solid; mp 222–223 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.28–7.26 (m, 5H), 7.14–7.07 (m, 5H), 6.99–6.98 (m, 2H), 6.74 (dd, *J*=1.2 and 7.8 Hz, 2H), 4.62 (d, *J*=14.8 Hz, 1H), 4.57 (d, *J*=14.8 Hz, 1H), 3.43 (d, *J*=10 Hz, 1H), 3.24 (d, *J*=10.4 Hz, 1H), 2.65 (s, 3H), 2.39 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.5, 150.9, 145.4, 141.2, 135.8, 134.0, 132.6, 128.7, 128.2, 128.0, 127.7, 127.6, 126.6,

126.0, 76.0, 61.2, 46.6, 21.9; IR (KBr): ν 3263, 1663, 1634, 1492, 1433, 1265, 708, 697 cm⁻¹; MS (*m/z*, EI): 405 (³⁷Cl, M⁺), 403 (³⁵Cl, M⁺), 388, 221, 120, 91 (100); calcd for C₂₅H₂₂ClNO₂: C, 74.34%; H, 5.49%; N, 3.47%; found: C, 74.26%; H, 5.58%; N, 3.33%.

4.3.6. Compound 3ha. Solid; mp 222–223 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.26–7.23 (m, 7H), 7.13–7.10 (m, 3H), 6.94–6.92 (m, 2H), 6.74 (d, *J*=6.8 Hz, 2H), 4.59 (s, 2H), 3.43 (d, *J*=10 Hz, 1H), 3.23 (d, *J*=10.8 Hz, 1H), 2.65 (s, 3H), 2.28 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.5, 150.9, 146.0, 141.2, 135.8, 134.0, 131.0, 128.7, 128.2, 127.7, 127.6, 126.6, 126.4, 120.8, 76.0, 61.1, 46.6, 21.9; IR (KBr): ν 3273, 3057, 2915, 1663, 1633, 1490, 1433, 760, 698 cm⁻¹; MS (*m/z*, EI): 449 (⁸¹Br, M⁺), 447 (⁷⁹Br, M⁺), 434, 432, 278, 221, 91 (100); calcd for C₂₅H₂₂BrNO₂: C, 66.97%; H, 4.95%; N, 3.12%; found: C, 67.24%; H, 4.94%; N, 3.08%.

4.3.7. Compound 3ia. Solid; mp 191–193 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.30–7.20 (m, 5H), 7.16–7.01 (m, 3H), 7.03 (d, *J*=8.8 Hz, 2H), 6.78 (d, *J*=6.4 Hz, 2H), 6.76 (d, *J*=8.8 Hz, 2H), 4.62 (d, *J*=14.8 Hz, 1H), 4.55 (d, *J*=14.4 Hz, 1H), 3.77 (s, 3H), 3.44 (d, *J*=10 Hz, 1H), 3.23 (d, *J*=10 Hz, 1H), 2.66 (s, 3H), 2.08 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.8, 158.5, 149.7, 141.4, 139.7, 136.0, 134.3, 128.7, 128.6, 128.2, 128.1, 127.6, 127.5, 126.6, 125.7, 113.4, 76.3, 61.0, 55.3, 46.5, 21.8; IR (KBr): ν 3332, 3057, 2915, 1662, 1627, 1512, 1435, 1242, 695 cm⁻¹; MS (*m/z*, EI): 399 (M⁺), 384, 252, 237, 135, 91 (100); HRMS-EI calcd for C₂₆H₂₅NO₃: 399.1834; found: 399.1837.

4.3.8. Compound 3ja. Solid; mp 81–83 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.33–7.23 (m, 6H), 7.17–7.15 (m, 3H), 7.01–6.99 (m, 4H), 6.77 (s, 1H), 5.98 (s, 1H), 4.75 (d, *J*=20 Hz, 1H), 4.53 (d, *J*=20 Hz, 1H), 3.54 (d, *J*=12 Hz, 1H), 3.28 (d, *J*=12 Hz, 1H), 2.19 (s, 1H), 0.14 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 166.7, 156.5, 147.4, 147.2, 140.7, 135.8, 128.7, 128.1, 128.0, 127.6, 126.9, 126.2, 125.8, 123.9, 76.0; IR (KBr): ν 3388, 3059, 3026, 2902, 1664, 1592, 1486, 1439, 1293, 1243 cm⁻¹; MS (*m/z*, EI): 427 (M⁺), 412 (100), 105, 91, 73, 65; HRMS-EI calcd for C₂₇H₂₉NO₂Si: 427.1968; found: 427.1971.

4.3.9. Compound 3ka. Solid; mp 196–198 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.66 (s, 1H), 7.37–7.24 (m, 7H), 7.17–7.10 (m, 7H), 4.70 (d, *J*=14.4 Hz, 1H), 4.27 (d, *J*=14.8 Hz, 1H), 4.16 (s, 1H), 3.61 (d, *J*=10.4 Hz, 1H), 3.36 (d, *J*=10.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.0, 142.0, 137.5, 135.5, 133.1, 132.7, 131.0, 129.5, 128.8, 128.4, 128.1, 127.8, 126.4, 74.8, 63.4, 47.1; IR (KBr): ν 3286, 3052, 3029, 2952, 2922, 1667, 1627, 1432, 739, 699 cm⁻¹; MS (*m/z*, EI): 391 (M⁺, ³⁷Cl), 389 (M⁺, ³⁵Cl), 327, 298, 286, 242, 155, 127, 85, 71, 57 (100), 43, 41; HRMS-EI calcd for C₂₄H₂₀ClNO₂: 389.1183; found: 389.1182.

4.3.10. Compound 3ab. Solid; mp 139–140 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.26–7.11 (m, 10H), 6.99 (d, *J*=7.8 Hz, 2H), 6.63 (d, *J*=8.1 Hz, 2H), 4.64 (d, *J*=14.7 Hz, 1H), 4.54 (d, *J*=14.7 Hz, 1H), 3.45 (d, *J*=9.9 Hz, 1H), 3.24 (d, *J*=9.9 Hz, 1H), 2.64 (s, 3H), 2.24 (s, 3H), 2.17 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 167.9, 149.9, 147.7, 138.4, 137.4, 136.0, 134.2, 128.9, 128.6, 128.1, 127.5, 126.9, 126.5, 124.5, 76.5, 60.8, 46.5, 21.8, 21.1; IR (KBr): ν 3416, 3058, 3026, 2910, 1657, 1633, 1510, 1482, 1440, 697 cm⁻¹; MS (*m/z*, EI): 383 (M⁺, 100), 368, 292, 221, 105, 91; calcd for C₂₆H₂₅NO₂: C, 81.43%; H, 6.57%; N, 3.65%; found: C, 81.40%; H, 6.67%; N, 3.56%.

4.3.11. Compound 3ac. Solid; mp 134–137 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.30–7.23 (m, 5H), 7.17–7.14 (m, 3H), 7.08–7.06 (m, 2H), 7.03 (t, *J*=7.6 Hz, 1H), 6.93 (d, *J*=7.6 Hz, 1H), 6.61 (d, *J*=7.6 Hz, 1H), 6.38 (s, 1H), 4.64 (d, *J*=14.8 Hz, 1H), 4.57 (d, *J*=14.8 Hz, 1H), 3.45 (d, *J*=9.6 Hz, 1H), 3.27 (d, *J*=10 Hz, 1H), 2.64 (s, 3H), 2.21 (s, 1H), 2.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 167.8, 150.2, 147.7, 141.1, 137.9, 136.0, 134.3, 128.6, 128.2, 128.1, 127.9, 127.5, 127.4, 126.8, 124.3, 123.4, 76.2, 60.8, 46.5, 21.7, 21.2; IR (KBr): ν 3385, 3051, 3030, 2914,

1668, 1635, 1496, 1483, 705, 699 cm^{-1} ; MS (m/z , EI) 383 (M^+), 368, 221, 159, 105, 91 (100); HRMS-EI calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_2$: 383.1885; found: 383.1887.

4.3.12. Compound 3ad. Solid; mp 147–148 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.29–7.11 (m, 10H), 6.68 (d, $J=8.4$ Hz, 2H), 6.60 (d, $J=8.4$ Hz, 2H), 4.63 (d, $J=14.8$ Hz, 1H), 4.55 (d, $J=14.8$ Hz, 1H), 3.72 (s, 3H), 3.45 (d, $J=10$ Hz, 1H), 3.25 (d, $J=10$ Hz, 1H), 2.64 (s, 3H), 2.24 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.9, 158.9, 149.7, 147.6, 136.0, 134.2, 133.6, 128.6, 128.2, 128.1, 128.0, 127.5, 126.9, 124.5, 113.6, 76.5, 60.9, 55.2, 46.5, 21.9; IR (KBr): ν 3398, 3034, 2914, 2837, 1656, 1627, 1510, 1440, 1247, 697 cm^{-1} ; MS (m/z , EI): 399 (M^+), 384, 175, 120, 105, 91(100); calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_3$: C, 78.14%; H, 6.31%; N, 3.51%; found: C, 78.10%; H, 6.48%; N, 3.27%.

4.3.13. Compound 3ae. Solid; mp 137–138 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.31–7.23 (m, 5H), 7.13–7.11 (m, 3H), 7.06–7.05 (m, 2H), 6.72 (d, $J=7.2$ Hz, 4H), 4.63 (d, $J=14.8$ Hz, 1H), 4.63 (d, $J=14.8$ Hz, 1H), 3.44 (d, $J=10.4$ Hz, 1H), 3.34 (d, $J=10.4$ Hz, 1H), 2.63 (s, 3H), 2.52 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 163.0, 160.5, 149.6, 146.4, 137.3, 135.9, 134.9, 128.7, 128.6, 128.2, 128.0, 127.6, 126.9, 124.5, 115.0, 114.8, 76.2, 61.6, 46.6, 21.9; ^{19}F NMR (MHz, CDCl_3): δ –114.1 to –112.2 (m); IR (KBr): ν 3408, 3028, 2912, 1658, 1635, 1508, 1484, 1440, 1225, 698 cm^{-1} ; MS (m/z , EI): 387 (M^+), 372, 225, 120, 91 (100), 372; calcd for $\text{C}_{25}\text{H}_{22}\text{FNO}_2$: C, 77.50%; H, 5.72%; N, 3.62%; found: C, 77.67%; H, 5.79%; N, 3.53%.

4.3.14. Compound 3af. Solid; mp 163–164 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.32–7.23 (m, 5H), 7.15–7.13 (m, 3H), 7.07–7.04 (m, 2H), 7.01 (d, $J=8.4$ Hz, 2H), 6.67 (d, $J=8.4$ Hz, 2H), 4.64 (d, $J=15.2$ Hz, 1H), 4.57 (d, $J=15.2$ Hz, 1H), 3.44 (d, $J=10.2$ Hz, 1H), 3.34 (d, $J=10$ Hz, 1H), 2.62 (s, 3H), 2.19 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.4, 149.3, 146.3, 139.8, 135.8, 135.0, 133.3, 128.7, 128.2, 128.1, 128.0, 127.6, 126.9, 124.5, 76.2, 61.5, 46.6, 21.7; IR (KBr): ν 3414, 3059, 2912, 1658, 1636, 1488, 1450, 1298, 701, 695 cm^{-1} ; MS (m/z , EI): 405 (^{37}Cl , M^+), 403 (^{35}Cl , M^+), 388, 120, 105, 91 (100); calcd for $\text{C}_{25}\text{H}_{22}\text{ClNO}_2$: C, 74.34%; H, 5.49%; N, 3.47%; found: C, 74.16%; H, 5.63%; N, 3.28%.

4.3.15. Compound 3ag. Solid; mp 159–160 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.46 (d, $J=7.2$ Hz, 2H), 7.40 (t, $J=7.2$ Hz, 2H), 7.34–7.24 (m, 8H), 7.11–7.10 (m, 5H), 6.81 (d, $J=8$ Hz, 2H), 4.61 (s, 2H), 3.46 (d, $J=10.4$ Hz, 1H), 3.32 (d, $J=10.4$ Hz, 1H), 2.70 (s, 3H), 2.46 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.7, 150.0, 146.8, 140.3, 140.1, 135.9, 134.6, 128.7, 128.6, 128.1, 127.9, 127.6, 127.4, 127.1, 126.9, 126.8, 126.6, 124.6, 76.3, 61.3, 46.6, 21.7; IR (KBr): ν 3358, 3050, 3028, 2897, 2848, 1658, 1612, 1478, 1264, 769, 755, 701 cm^{-1} ; MS (m/z , EI): 445 (M^+), 430, 221, 120, 105, 91 (100); calcd for $\text{C}_{31}\text{H}_{27}\text{NO}_2$: C, 83.57%; H, 6.11%; N, 3.14%; found: C, 83.48%; H, 6.32%; N, 3.00%.

4.3.16. Compound 3ah. Solid; mp 184–189 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.87 (s, 1H), 7.58 (s, 1H), 7.26–7.35 (m, 5H), 7.16–7.19 (m, 2H), 6.97 (d, $J=6.4$ Hz, 5H), 4.72 (d, $J=14.4$ Hz, 1H), 4.57 (d, $J=14.8$ Hz, 1H), 3.49 (d, $J=11.2$ Hz, 1H), 3.44 (d, $J=11.2$ Hz, 1H), 3.12 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.2, 149.0, 147.2, 144.1, 142.8, 136.0, 135.7, 133.2, 128.8, 128.4, 128.2, 127.8, 127.7, 126.7, 124.7, 122.6, 121.8, 75.7, 62.8, 46.8, 21.5; IR (KBr): ν 3439, 3081, 3028, 2919, 2866, 1658, 1637, 1525, 1348, 1265, 699 cm^{-1} ; MS (m/z , EI): 414 (M^+), 399, 120, 105, 91 (100); calcd for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_4$: C, 72.45%; H, 5.35%; N, 6.76%; found: C, 72.10%; H, 5.38%; N, 6.68%.

4.3.17. Compound 3ai. Solid; mp 147–148 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, $J=7.2$ Hz, 1H), 7.59 (d, $J=8.4$ Hz, 1H), 7.42–7.39 (m, 3H), 7.31–7.24 (m, 5H), 7.11–7.05 (m, 6H), 6.94 (d, $J=8.4$ Hz, 1H), 4.67 (d, $J=14.8$ Hz, 1H), 4.57 (d, $J=14.8$ Hz, 1H), 3.46 (d, $J=10$ Hz, 1H), 3.29 (d, $J=10$ Hz, 1H), 2.73 (s, 3H), 2.18 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.8, 149.8, 147.7, 138.6, 135.9, 134.9, 132.4, 132.2, 128.7,

128.2, 128.1, 128.0, 127.6, 127.5, 126.9, 126.4, 126.3, 125.6, 124.6, 124.4, 76.4, 60.9, 46.6, 21.6; IR (KBr): ν 3365, 3059, 3026, 2935, 2910, 1668, 1645, 1481, 1430, 1286, 1264, 747, 700 cm^{-1} ; MS (m/z , EI): 419 (M^+), 404, 195, 91 (100); calcd for $\text{C}_{29}\text{H}_{25}\text{NO}_2$: C, 83.03%; H, 6.01%; N, 3.34%; found: C, 82.97%; H, 6.18%; N, 3.10%.

4.4. Synthesis of dimethyl 2-(but-2'-ynyl)-2-(benzoylmethyl) malonate (11)

To the solution of NaH (4.5 mmol) in THF (10 mL), dimethyl 2-(2-butynyl)malonate (2.3 mmol) was added dropwise at -10 °C. After the reaction was stirred for 20 min the solution of ω -bromoacetophenone (2.4 mmol) in THF was added dropwise. Then the mixture was refluxed for 5 h as monitored by TLC. The reaction was quenched by 5 mL of saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethylether several times. The combined organic layer was dried by MgSO_4 . The mixture was concentrated and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as the eluent to afford the desired product in 50% yield.

4.5. Synthesis of (Z)-dimethyl 3-hydroxy-3-phenyl-4-(1-phenylethylidene) cyclopentane-1,1-dicarboxylate (3la)

$\text{Pd}(\text{OAc})_2$ (5 mol %), bpy (6 mol %), and DCE (2 mL) was added into a dried Schlenk tube, then the mixture was stirred at 80 °C for 10 min. The substrate **3la** (0.1 mmol), phenylboronic acid (1.3 equiv), KF (1.5 equiv), and H_2O (0.1 mL) were added subsequently, then reacted at 80 °C oil bath until the consumption of **3la** as monitored by TLC. Then the reaction mixture was concentrated and purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as the eluent to afford the desired product in 66% yield.

4.5.1. Compound 3la²¹. Solid; mp 86–88 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.01–6.98 (m, 5H), 6.95–6.91 (m, 3H), 6.68–6.65 (m, 2H), 3.82 (s, 3H), 3.70 (s, 3H), 3.65 (dq, $J=17$ and 0.8 Hz, 1H), 3.16 (dq, $J=16.8$ and 2 Hz, 1H), 2.78–2.69 (m, 2H), 2.45 (s, 1H), 2.01 (q, $J=1.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.8, 171.8, 146.2, 141.9, 141.5, 134.9, 127.7, 127.6, 127.2, 126.1, 125.9, 125.3, 82.0, 57.5, 53.2, 53.0, 52.9, 40.5, 23.9; IR (KBr): ν 3567, 3057, 2955, 2852, 1733, 1600, 1494, 1436, 1257, 761, 699 cm^{-1} ; MS (m/z , ESI): 362 ($\text{M}^+ - \text{H}_2\text{O}$), 302 (100); HRMS-ESI calcd for $\text{C}_{23}\text{H}_{22}\text{O}_4$ ($\text{M}^+ - \text{H}_2\text{O}$): 362.1518; found: 362.1523.

Acknowledgements

The National Basic Research Program of China 2006CB806105 is acknowledged. We also thank the National Natural Science Foundation of China (20732005, 20872158) and Chinese Academy of Sciences for financial support.

Supplementary data

The spectroscopic and analytic data of the new compounds are included in the Supplementary data. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.090. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

- Geissman, T. A.; Irwin, M. A. *Pure Appl. Chem.* **1970**, *21*, 167.
- Ikuta, H.; Shirota, H.; Kobayashi, S.; Yamagishi, Y.; Yamada, K.; Yamatsu, I.; Katayama, K. *J. Med. Chem.* **1987**, *30*, 1995.
- Patra, R.; Maiti, S. B.; Chatterjee, A.; Chakravarty, A. K. *Tetrahedron Lett.* **1991**, *32*, 1363.

4. Moloney, M. G. *Nat. Prod. Rep.* **1999**, *16*, 485.
5. (a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230; (b) Reddy, L. R.; Fournier, J. F.; Reddy, B. V. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974; (c) Reddy, L. R.; Fournier, J. F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699.
6. (a) Elford, T. G.; Agnieszka, U. L.; Gianfranco, D. P.; Wright, G. D.; Hall, D. G. *J. Comb. Chem.* **2009**, *11*, 155; (b) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516; (c) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765; (d) Lettan, R. B., II; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294; (e) Krawczyk, H.; Albrecht, L.; Wojciechowski, J.; Wolf, W. M.; Krajewska, U.; Rozalski, M. *Tetrahedron* **2008**, *64*, 6307; (f) Alami, N. E.; Belaud, C.; Villieras, J. *Tetrahedron Lett.* **1987**, *28*, 59; (g) Dembélé, Y. A.; Belaud, C.; Hitchcock, P.; Villieras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351; (h) Dembélé, Y. A.; Belaud, C.; Villieras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511; (i) Nyzam, V.; Belaud, C.; Zammattio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1992**, *7*, 1835; (j) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376; (k) Tanaka, K.; Yoda, H.; Kaji, A. *Synthesis* **1985**, 84; (l) Béji, F.; Lebreton, J.; Villieras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959; (m) Lee, K. Y.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 2007; (n) Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058; (o) Jiang, H.; Ma, S.; Zhu, G.; Lu, X. *Tetrahedron* **1996**, *52*, 10945; (p) Xie, X.; Lu, X.; Liu, Y.; Xu, W. *J. Org. Chem.* **2001**, *66*, 6545; (q) Xu, W.; Kong, A.; Lu, X. *J. Org. Chem.* **2006**, *71*, 3854.
7. (a) Duan, H.; Xie, J.; Shi, W.; Zhang, Q.; Zhou, Q. *Org. Lett.* **2006**, *8*, 1479; (b) Shukla, P.; Cheng, C. *Org. Lett.* **2006**, *8*, 2867; (c) Quan, L.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827; (d) Quan, L.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545.
8. (a) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, 1637; (b) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *595*, 31; (c) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128; (d) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584; (e) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307; (f) Duan, H.; Jia, Y.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 2567; (g) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092.
9. (a) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339; (b) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238.
10. (a) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343; (b) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765; (c) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987; (d) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504; (e) Dai, H.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 3478; (f) Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077; (g) Yu, X.; Lu, X. *Org. Lett.* **2009**, *11*, 4366.
11. (a) Song, J.; Shen, Q.; Xu, F.; Lu, X. *Org. Lett.* **2007**, *9*, 2947; (b) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131; (c) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 108.
12. (a) Zhu, G.; Tong, X.; Cheng, J.; Sun, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1712; (b) Xie, X.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 8415; (c) Stamm, H.; Baumann, T. *Pharmazie* **1999**, *54*, 885.
13. The structure of the product **3aa** was confirmed by X-ray crystallography. Deposit number of compound **3aa** from Crystallographic Data Centre: CCDC 234945. Copies of the data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.
14. (a) Li, P.; Xu, J. *J. Org. Chem.* **2000**, *65*, 2951; (b) Balli, H.; Kersting, F. *Liebigs Ann. Chem.* **1961**, 647, 1.
15. Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170.
16. (a) Shang, G.; Liu, D.; Allen, S. E.; Yang, Q.; Zhang, X. *Chem.—Eur. J.* **2007**, *13*, 7780; (b) Hyde, J. F.; Browning, E.; Adams, R. *J. Am. Chem. Soc.* **1928**, *50*, 2287.
17. Fourrey, J.; Beauhaire, J.; Yuan, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1841.
18. Simmross, F. M.; Weyerstahl, P. *Synthesis* **1981**, 72.
19. Shtacher, G.; Rubinstein, R.; Somani, P. *J. Med. Chem.* **1978**, *21*, 678.
20. Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059.
21. Miura, T.; Shimada, M.; Murakami, M. *Tetrahedron* **2007**, *63*, 6131.