Tetrahedron 67 (2011) 1231–1237

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tandem allylic amination/ring-opening/oxa-Michael addition reactions of chromone-derived Morita–Baylis–Hillman acetates with amines

Chen Wu †, Hao Zeng †, Li Liu *, Dong Wang, Yongjun Chen

Beijing National Laboratory (BNLMS), Laboratory for Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, PR China

ARTICLE INFO

Article history:
Received 20 September 2010
Received in revised form 9 November 2010
Accepted 26 November 2010
Available online 1 December 2010

Keywords:
MBH acetates
Tandom reaction
Amines

ABSTRACT

The reaction of chromone-derived Morita–Baylis–Hillman acetates with amines was developed via tandem allylic amination/chromone ring-opening/oxa-Michael addition to provide 2-substituted-3-aminomethy-lene-chromans in convenient and efficient way, and subsequent applied in the synthesis of benzopyranylpyrimidine compounds. Various amines exhibited different reactivities depending on their molecular structural characteristics.

1. Introduction

Morita–Baylis–Hillman adducts are attracting much attentions in organic synthesis due to their ready availability and multi-functionalities.[1] Similarly, aza-Baylis–Hillman reaction can provide β-aminocarbonyl compounds, which possess both allyl amino and Michael acceptor units in an identical molecule and is very important in the synthesis of bioactive molecules and natural products.[1,2] Although aza-Baylis–Hillman reaction has made great progresses, it still remains some shortcoming, such as long reaction time and low yields, moreover second amines are seldom used.[3] Alternatively, allylic amination of Morita–Baylis–Hillman (MBH) adducts could provide various aza-Byalis–Hillman analogues easily.[4] In most cases, acyclic MBH adducts were used.

Cyclic MBH adducts derived from cycloenones exhibited the reactive properties different from that of the acyclic adducts, which could be used to generate fused cyclic frameworks.[5] Recently, we reported an AgOTf-catalyzed highly α-regioselective allylic substitution of cyclic MBH acetate with indoles,[6] and tunable regioselective control (α or γ-selection) when MBH alcohols were used and iodine as catalyst.[7] Chan and co-workers[8] reported iron(III) catalyzed nucleophilic α-substitution of cyclic MBH alcohols with several nucleophiles except amine, a N-nucleophile. It was noteworthy that the allylic amination of cyclic MBH adducts derived from cyclopentenones and cyclohexenones with aromatic amines also provide α-selective products under the catalysis of $In(OTf)_3$[9] or $FeCl_3$.[10] Chromone-derived MBH adducts bearing cyclic structural unit have been used in the syntheses of many heterocycles, such as quinoline derivatives and azepinoindoles (Fig. 1).[6,11] We envisioned that the investigations of the allylic amination of cyclic MBH acetates derived from chromone should be very interesting and valuable to develop a novel synthetic approach to heterocycles.

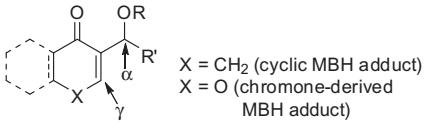


Fig. 1. Cyclic MBH adducts.

Moreover, 3-aminomethylchromones (**A**)[12] as well as their derivatives, 3-aminomethylenechromans (**B**)[13] have important biological activities and are also interesting as a scaffold in the synthesis of versatile benzopyranyl heterocycle libraries in drug discovery (Fig. 2). It was found that 3-pyrrolidine substitute

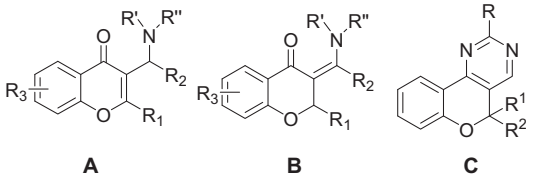


Fig. 2. 3-Aminomethylchromone derivatives.

* Corresponding author. Tel.: +86 10 62554614; fax: +86 10 62554449; e-mail address: lliu@iccas.ac.cn (L. Liu).

† These authors made equal contributions to the paper.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.089

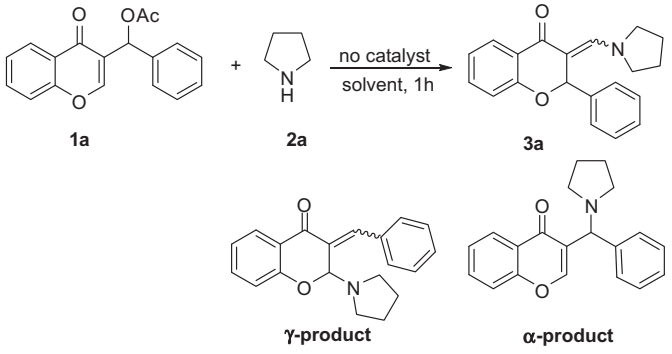
chromones could be used as a key intermediate for the synthesis of benzopyranylpyrimidine (**C**),[14] which exhibit great importance of biological activities. Therefore, to develop an efficient method to construct the intermediates is still desired.

To continue our interests in the nucleophilic substitution reaction of cyclic MBH adducts, we describe herein the results of the tandem reaction between chromone-derived MBH acetates and amines in a one pot process. In the process, a cascade allylic amination/ring-opening/oxa-Michael cyclization was involved to provide 3-aminomethylenechromans in high yields and subsequent this protocol was used in the synthesis of benzopyranylpyrimidine compounds.

2. Results and discussion

2.1. The reaction of MBH acetates with amines

In general, for the allylic substitution of MBH adducts, efficient catalyst was required to promote the reaction. Considering excellent leaving-ability of the OAc group in nucleophilic substitution reaction, the catalyst-free reaction conditions were employed in the allylic amination of the chromone-derived MBH acetates with amines. According to the reference procedure, the chromone-derived MBH acetates were prepared through the Baylis–Hillman reaction of chromones with aldehydes. Initially, the reaction of (4-oxo-4*H*-chromen-3-yl)(phenyl)methyl acetate (**1a**) and pyrrolidine (**2a**) was carried out in refluxing THF for 1 h in the absence of any catalyst and additives. To our surprise, neither α- nor γ-product was detected in the reaction mixture, and the tandem reaction product, 2-phenyl-3-aminomethylene-chroman **3a** was formed exclusively in 57% yield (Scheme 1).



Scheme 1. Reaction of **1a** with **2a**.

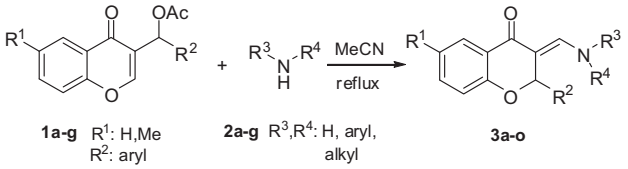
Subsequently, solvent screening was performed by means of the reaction of **1a** with **2a** under the same conditions, and the results are summarized in Table 1. As shown in Table 1, the tandem reaction can be achieved successfully in various solvents. In dichloromethane (DCM), the yield of **3a** was decreased to 33% (entry 2); while in the high boiling point solvent, such as toluene, the yield was only slightly increased to 62%. In EtOH, the reaction gave moderate yield of 58%. To our great delight, the yield can be improved to 86% when MeCN was employed as a solvent. Furthermore, water was also used as a solvent and the yield of **3a** was as good as MeCN. However, water was not widely suitable to other substrates of chromone-derived MBH acetates. So MeCN was chosen as the solvent eventually.

Table 1
Solvent effect on the reaction of **1a** with **2a**[a]

Entry	Solvent	Temp (°C)	Yield of **3a** (%)[b]
1	THF	Reflux	57
2	DCM	Reflux	33
3	EtOH	Reflux	58
4	Toluene	Reflux	62
5	MeCN	Reflux	86
6	Water	80	86

[a] **1a** (0.2 mmol), **2a** (0.3 mmol), solvents (2 mL), 1 h.
[b] Isolated yield.

With optimal conditions on hands, we examined the substrate-suitable scope of the tandem reaction (Scheme 2, Table 2). Cyclic amines including pyrrolidine (**2a**) and piperidine (**2b**) as well as imidazole (**2c**) were employed in the reactions with MBH acetates (**1a**–**f**) without the use of catalyst to give the corresponding products (**3a**–**j**) in good to excellent yields (Table 2, entries 1–9), but with different reaction times. Neither α- nor γ-products were detected in the reaction mixtures. Primary amine, such as benzyl amine (**2d**) and alkylamine (**2e**) exhibited very high reactivities: the shortest reaction time (1.5 h) and excellent yields (**3l**, 90% and **3m**, 93%) (entries 12 and 13). However, for aromatic amine, such as aniline (**2f**) under the similar conditions the reaction with **1a** provided the product **3n** in low yield (49%, Table 2, entry 14) even prolonging reaction time to 48 h, which probably was attributed to the weak nucleophilicity of aromatic amine. Fortunately, if $In(OTf)_3$ was used as a catalyst (10 mol %) in the reaction, the yield of **3n** increased remarkably to 95% (entry 15). When dipropylamine (**2g**) was employed in the reaction with **1a** in the presence of $In(OTf)_3$ (10 mol %) in refluxing MeCN, after long reaction time (72 h) relatively low yield (50%) of the product **3o** was obtained and 43% of starting MBH acetate **1a** was recovered (entry 16). The reason leading to the low reactivity probably is the steric effect of two substituents on the nitrogen atom of acyclic secondary aliphatic amine.



Scheme 2. Tandem reaction of chromone-derived MBH acetates with amines.

The molecular structure of the tandem reaction product **3a**–**k** and **3o** from the reactions of secondary amines was further confirmed by X-ray crystallography analysis of **3f** (Fig. 3).[15] Based on the results (*E*)-configuration of the newly formed double bond could be determined. For the products (**3l**–**n**) yielded from primary amine, the configuration of the newly formed double bound was determined as (*Z*) owing to the formation of hydrogen bond between N–H and C=O group.[16]

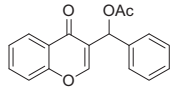
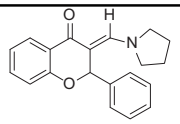
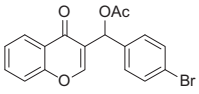
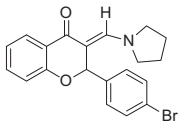
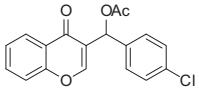
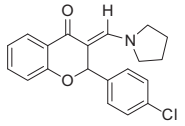
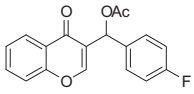
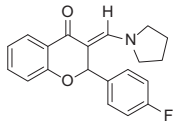
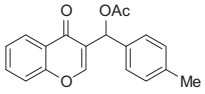
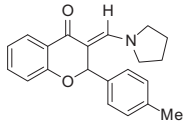
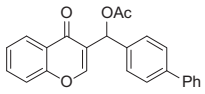
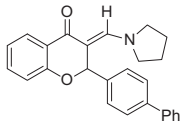
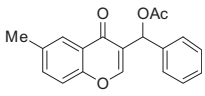
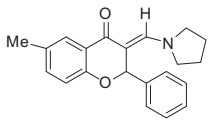
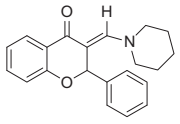
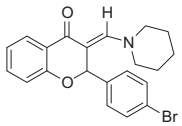
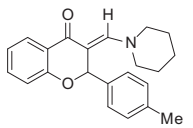
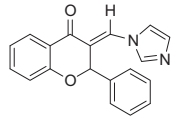
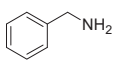
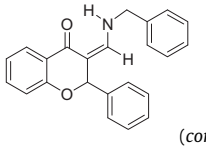
2.2. The proposed mechanism of the reaction

The plausible mechanism of the tandem reaction of MBH acetates with amine was proposed shown in Scheme 3, taking secondary amine as an example. The MBH acetate was attacked by *N*-nucleophile to form intermediate **I** through allylic amination accompanied with the elimination of OAc group. Subsequently, intermediate **I** underwent chromone ring-opening to yield an active iminum ion **II**, which was followed by intramolecular oxa-Michael addition to provide 2-substituted-3-aminomethylenechroman **3**.

2.3. Synthesis of benzopyranylpyrimidines

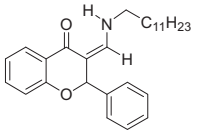
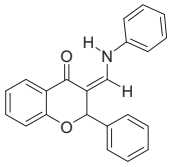
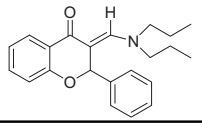
According the reference procedure,[14d] **3a** can react with benzamidine hydrochloride (**4a**, R′=Ph) in refluxing EtOH by using

Table 2
Allylic amination of MBH acetates (**1**) with amines (**2**)[a]

Entry	MBH acrtate	Amine	Time (h)	Product	Yield (%)[b]
1	**1a** 	**2a** 	3	**3a** 	86
2	**1b** 	**2a**	3	**3b** 	86
3	**1c** 	**2a**	3	**3c** 	75
4	**1d** 	**2a**	3	**3d** 	70
5	**1e** 	**2a**	3	**3e** 	66
6	**1f** 	**2a**	3	**3f** 	72
7	**1g** 	**2a**	3	**3g** 	78
8	**1a**	**2b** 	3	**3h** 	87
9	**1b**	**2b**	3	**3i** 	70
10	**1e**	**2b**	4	**3j** 	68
11	**1a**	**2c** 	72	**3k** 	93
12	**1a**	**2d** 	1.5	**3l** 	90

(*continued on next page*)

Table 2 (*continued*)

Entry	MBH acrtate	Amine	Time (h)	Product	Yield (%)[b]
13	**1a**	**2e** $C_{12}H_{25}HN_2$	1.5	**3m** 	93
14	**1a**	**2f** 	48	**3n** 	49
15	**1a**	**2f**	36	**3n**	95[c]
16	**1a**	**2g** 	72	**3o** 	50[c]

[a] **1**/**2**=1:1.5, in refluxing CH_3CN.
[b] Isolated yield.
[c] With $In(OTf)_3$ (10 mol %) as a catalyst.

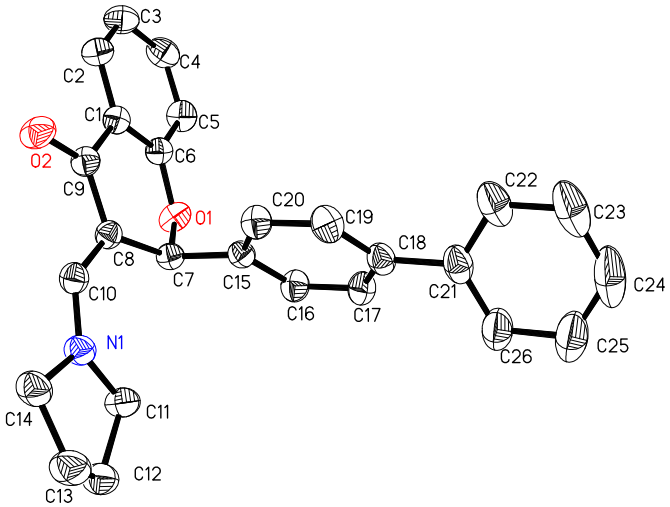
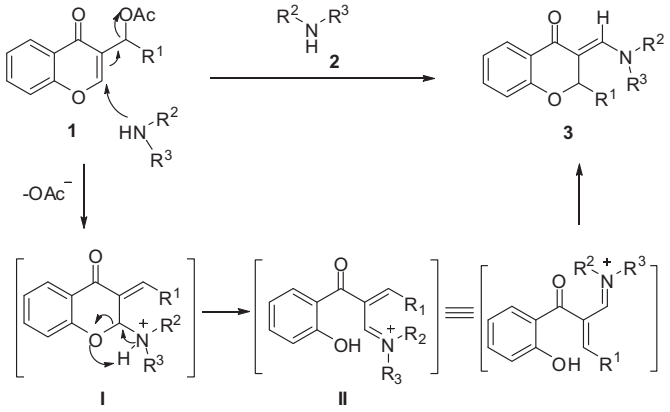


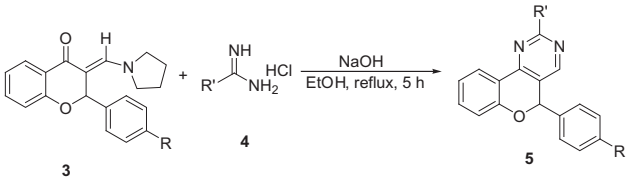
Fig. 3. ORTEP drawing of **3f** with thermal cllipsoids at 30% possibility level.



Scheme 3. Proposed mechanism of the reaction of chromone-derived MBH acetate with secondary amine.

NaOH as a base for emission of the free amine, which participated in the reaction with **3a**, to afford benzopyranylpyrimidine **5a** in yield 85% (Table 3, entry 1). Similarly, **3d**, **3f** and **3a** can undergo the same reaction with **4a** and **4b**, respectively, giving corresponding products **5b**–**d** in good yields (Table 3).

Table 3
Synthesis of benzopyranylpyrimidine compounds **5**[a]



Entry	**3** (R)	Diamine (R′)	Yield (%)[b]
1	**3a**, H	**4a**, Ph	**5a**, 85
2	**3d**, F	**4a**, Ph	**5b**, 75
3	**3f**, Me	**4a**, Ph	**5c**, 65
4	**3a**	**4b**, NH_2	**5d**,[14b] 78

[a] **3**/**4**=1:3.
[b] Isolated yield.

3. Conclusion

In summary, we developed the reaction of chromone-derived Morita–Baylis–Hillman acetates with amines for the synthesis of 2-substituted-3-aminomethylenechromans. This protocol combined allylic amination, ring-opening, Michael cyclization in a one pot process. Various amines exhibited the reactivities with big differences depending on their molecular structural characteristics. A tentative mechanism for the tandem reactions was proposed. Investigation of the tandem reactions and their application in the synthesis of biologically active compounds is ongoing.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on Bruker-AV 300 spectrometer and chemical shift reported in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. IR spectra were

recorded on a Bruker tensor 27 infrared spectrometer. HRMS spectra were recorded on GCT-Mass Micromass spectrometer. Melting points were measured on Beijing-Tiker X-4 apparatus without correction. All reactions were carried out in oven dried flasks. Common reagents were purchased from commercial sources and were used without further purification. The MBH acetates (**1a**–**g**) were prepared according to literature methods.[17]

4.2. Typical experimental procedures for the reaction of MBH acetates with amines

To a solution of (4-oxo-4*H*-chromen-3-yl)(phenyl)-methyl acetate (**1a**, 58 mg, 0.2 mmol) in MeCN (2 mL) at room temperature was added pyrrolidine (**2a**, 17 μL, 0.3 mmol), followed by stirring at the temperature of refluxing MeCN for 3 h upon completion of the reaction as judged by TLC. Then the mixture was cooled to room temperature and evaporated under vacuum to give crude product, which was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=1:1) to afford a white solid **3a** (52 mg, 86% yield).

*4.2.1. (E)-2-Phenyl-3-(pyrrolidin-1-ylmethylene) chromone (**3a**).* Yellow solid, mp 172–174 °C. FTIR(KBr): ν_{max} 3053, 2960, 2919, 2858, 1649, 1601, 1466, 1277, 1218, 1150, 1100, 1022, 801, 753, 695, 499 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.82–7.80 (m, 1H), 7.38–7.36 (m, 2H), 7.21–7.12 (m, 4H), 6.83–6.74 (m, 2H), 6.60 (s, 1H), 3.51 (m, 2H), 3.40 (m, 2H), 1.81–1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 164.0, 160.7, 157.6, 145.6, 137.5, 127.5, 133.8, 129.6, 127.0, 123.8, 121.1, 117.7, 115.3, 115.0, 100.8, 75.7, 25.3. HRMS(EI): *m*/*z* calcd for $C_{20}H_{19}NO_2$: 305.1416 (M^+), found 305.1417.

*4.2.2. (E)-2-(4-Bromophenyl)-3-(pyrrolidin-1-ylmethylene) chroman-4-one (**3b**).* Yellow oil. FTIR(film): ν_{max} 3445, 3214, 3169, 3154, 3127, 1644, 1400, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.80–7.77 (m, 1H), 7.31–7.12 (m, 5H), 6.84–6.80 (m, 1H), 6.73–6.71 (m, 1H), 6.51 (s, 1H), 3.50–3.47 (m, 2H), 3.34 (m, 2H), 1.80–1.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 164.0, 160.7, 157.6, 145.6, 137.5, 127.5, 133.8, 129.6, 127.0, 123.8, 121.1, 117.7, 115.3, 115.0, 100.8, 75.7, 25.3. HRMS(EI): *m*/*z* calcd for $C_{20}H_{18}BrNO_2$: 383.0521 (M^+), found 383.0524.

*4.2.3. (E)-2-(4-Chlorophenyl)-3-(pyrrolidin-1-ylmethylene)chroman-4-one (**3c**).* Yellow solid, mp 134–135 °C. FTIR(film): ν_{max} 3220, 3191, 3179, 3165, 3152, 3132, 3123, 3116, 3109, 3095, 1648, 1587, 1549, 1406, 1336, 1307, 1008, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.90–7.87 (m, 1H), 7.40–7.38 (m, 2H), 7.32–7.23 (m, 3H), 6.95–6.90 (m, 1H), 6.84–6.81 (m, 1H), 6.63 (s, 1H), 3.64–3.57 (m, 2H), 3.46 (m, 2H), 1.96–1.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 157.6, 145.7, 140.2, 133.9, 133.8, 129.2, 128.5, 127.0, 123.8, 121.4, 117.7, 100.6, 75.7, 25.3. HRMS (EI): *m*/*z* calcd for $C_{20}H_{18}ClNO_2$: 339.1026 (M^+), found 339.1026.

*4.2.4. (E)-2-(4-Fluorophenyl)-3-(pyrrolidin-1-ylmethylene) chroman-4-one (**3d**).* Yellow solid, mp 173–174 °C. FTIR(film): ν_{max} 3227, 3146, 1644, 1551, 1503, 1394, 1334, 1304, 1222, 1002, 762, 490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.90–7.87 (m, 1H), 7.44–7.40 (m, 2H), 7.30–7.23 (m, 1H), 6.96–6.87 (m, 3H), 6.82–6.80 (m, 1H), 6.64 (s, 1H), 3.60–3.53 (m, 2H), 3.43–3.41 (m, 2H), 1.90–1.80 (m,4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 164.0, 160.7, 157.6, 145.6, 137.5, 127.5, 133.8, 129.6, 127.0, 123.8, 121.1, 117.7, 115.3, 115.0, 100.8, 75.7, 25.3. HRMS (EI): *m*/*z* calcd for $C_{20}H_{18}FNO_2$: 323.1322 (M^+), found 323.1325.

*4.2.5. (E)-3-(Pyrrolidin-1-ylmethylene)-2-p-tolyl-chroman-4-one (**3e**).* Yellow oil, mp 101–104 °C. FTIR(film): ν_{max} 3117, 1648, 1554, 1457, 1386, 1334, 1304, 1009, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.81–7.78 (m, 1H), 7.25–7.23 (m, 2H), 7.18–7.12 (m, 1H), 6.98–6.96 (m, 2H), 6.81–6.71 (m, 2H), 6.55 (s, 1H), 3.50–3.45 (m, 2H), 3.35–3.32 (m, 2H), 2.16 (s, 3H), 1.79–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.9, 157.9, 145.4, 138.8, 137.6, 133.6, 129.0, 127.8, 126.9, 123.9, 121.0, 117.8, 101.2, 76.3, 51.6, 25.3, 21.0. HRMS (EI): *m*/*z* calcd for $C_{21}H_{21}NO_2$: 319.1572 (M^+), found 319.1569.

*4.2.6. (E)-2-(Biphenyl-4-yl)-3-(pyrrolidin-1-ylmethylene) chroman-4-one (**3f**).* Yellow solid, mp 191–193 °C. FTIR(film): ν_{max} 3227, 3212, 3178, 3161, 3149, 3133, 3117, 3019, 1628, 1399, 509 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (s,1H), 7.93–7.89 (m, 1H), 7.58–7.49 (m, 6H), 7.42–7.38 (m, 2H), 7.33–7.27 (m, 2H),6.95–6.88 (m, 2H), 6.72 (s, 1H), 3.61–3.60 (m, 2H), 3.48–3.45 (m, 2H), 1.91–1.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.1, 157.9, 145.6, 140.8, 140.7, 140.5, 133.8, 128.7, 127.4, 127.1, 127.0, 123.9, 121.2, 117.8, 101.0, 76.2, 25.4. HRMS (EI): *m*/*z* calcd for $C_{26}H_{23}NO_2$: 381.1729 (M^+), found 381.1726.

*4.2.7. (E)-6-Methyl-2-phenyl-3-(pyrrolidin-1-ylmethylene) chroman-4-one (**3g**).* Yellow solid, mp 101–104 °C. FTIR(film): ν_{max} 3444, 3059, 1646, 1548, 1420, 1382, 1331, 1139, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.60–7.59 (m, 1H), 7.37–7.35 (m, 2H), 7.21–7.11 (m, 3H), 7.00–6.97 (m, 1H), 6.67–6.64 (m, 1H), 6.56 (s, 1H), 3.54–3.47 (m, 2H), 3.38–3.35 (m, 2H), 2.14 (s, 3H), 1.84–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.1, 155.8, 145.4, 141.8, 134.6, 130.4, 128.3, 127.8, 127.8, 126.9, 123.4, 117.5, 25.3, 20.5. HRMS (EI): *m*/*z* calcd for $C_{21}H_{21}NO_2$: 319.1572 (M^+), found 319.1572.

*4.2.8. (E)-2-Phenyl-3-(piperidin-1-ylmethylene) chroman-4-one (**3h**).* Yellow oil. FTIR(film): ν_{max} 3219, 3205, 3193, 3178, 3164, 3150, 3136, 3123, 3110, 1638, 1539, 1465, 1399, 1320, 763, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.81–7.78 (m, 2H), 7.40–7.38 (m, 2H), 7.21–7.12 (m, 4H), 6.82–6.78 (m, 1H), 6.73–6.70 (m, 1H), 6.43 (s, 1H), 3.25 (m, 4H), 1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0, 157.7, 148.4, 140.3, 133.6, 128.3, 128.2, 128.0, 126.9, 123.7, 121.1, 117.6, 100.0, 76.7, 52.9, 26.423.7. HRMS(EI): *m*/*z* calcd for $C_{21}H_{21}NO_2$: 319.1572 (M^+), found 319.1575.

*4.2.9. (E)-2-4-Bromophenyl-3-(piperidin-1-ylmethylene) chroman-4-one (**3i**).* Yellow solid, mp:121–124 °C. FTIR(film): ν_{max} 3422, 2935, 2856, 1637, 1586, 1536, 1367, 1329, 1257, 1203, 996, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88–7.85 (m, 2H), 7.37 (q, 4H, *J*=0.9 Hz), 7.29–7.23 (m, 1H), 6.90 (t, 1H, *J*=0.9 Hz), 6.80 (d, 1H, *J*=0.9 Hz), 6.44 (s, 1H), 3.34 (d, 4H, *J*=0.3 Hz), 1.60 (d, 6H, *J*=0.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 157.4, 148.5, 139.4, 133.7, 131.5, 129.8, 126.9, 123.6, 122.4, 121.4, 117.6, 99.4, 77.0, 52.9, 26.3, 23.6. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}BrNO_2$: 398.0745 (M^+), found 398.0746.

*4.2.10. (E)-3-(Piperidin-1-ylmethylene)-2-p-tolyl-chroman-4-one (**3j**).* Yellow oil. FTIR(film): ν_{max} 3452, 2922, 2852, 1725, 1646, 1547, 1461, 1324, 1257, 1202, 1099, 1023, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ 7.36–7.27 (m, 2H), 7.25 (d, 2H, *J*=4.8 Hz), 7.24–7.21 (m, 1H), 7.06 (d, 2H, *J*=8.1 Hz), 6.90–6.85 (m, 1H), 6.78 (d, 1H, *J*=8.4 Hz), 6.47(s, 1H), 3.34 (d, 4H, *J*=2.1 Hz), 2.26 (s, 3H), 1.60–1.54 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0.157.7, 148.3, 137.9, 137.3, 133.6, 129.0, 128.0, 126.9, 123.7, 121.1, 117.6, 100.2, 77.0, 52.9, 26.3, 23.7, 21.0. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{23}NO_2$: 334.1793(M^-), found 334.1797.

*4.2.11. (E)-2-Phenyl-3-(imidazol-1-ylmethylen)chroman-4-one (**3k**).* White oil. FTIR(film): ν_{max} 3410, 3110, 1644, 1572, 1495, 1465, 1400, 1351, 1319, 1216, 1075, 760, 741, 723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ 7.61–7.56(m, 1H), 7.46(s, 1H), 7.36–7.24(m, 6H), 7.08–7.01(m, 3H), 6.86(s, 1H), 6.71(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 156.2, 155.3, 137.1, 136.8, 134.2, 129.4, 129.1, 128.6,

127.3, 126.0, 125.7, 124.0, 123.5, 119.1, 118.2, 56.68. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{14}N_2O_2$ 303.1125(M^-), found: 303.1125.

*4.2.12. (Z)-3-[(Benzylamino)methylene]-2-phenylchroman-4-one (**3l**).* Yellow solid, mp 146–148 °C. FTIR(film): ν_{max} 3242, 3083, 3061, 3025, 2928.38, 2854, 1953, 1644, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.40–10.36 (t, 1H, *J*=5.1 Hz), 7.91–7.88 (d, 1H, *J*=7.4 Hz), 7.46–7.43 (m, 2H), 7.39–7.24 (m, 7H), 7.20–7.17 (m, 2H), 7.02–6.97 (t, 1H, *J*=7.4 Hz), 6.93–6.90 (d, 1H, *J*=8.2 Hz), 6.40–6.35 (d, 1H, *J*=12.6 Hz), 5.96 (s, 1H), 4.32–4.30 (d, 2H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.3, 158.7, 1511.5, 139.5, 137.5, 134.0, 128.9, 28.6, 128.5, 127.9, 127.8, 127.1, 126.4, 123.9, 121.5, 117.6, 102.4, 81.2, 52.9. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}NO_2$: 342.1486 (M^+), found 342.1489. $C_{22}H_{17}NO_2$: 327.1259 (M^+), found 327.1262.

*4.2.13. (Z)-3-[(Dodecylamino)methylene]-2-phenylchro-man-4-one (**3m**).* Colourless oil. FTIR(film): ν_{max} 3236, 3062, 2922, 2852, 1647, 1607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.20–10.16 (t, 1H, *J*=5.8 Hz), 7.92–7.89 (d, 1H, *J*=7.4 Hz), 7.47–7.32 (m, 6H), 7.03–6.98 (t, 1H, *J*=7.4 Hz), 6.93–6.90 (d, 1H, *J*=8.2 Hz), 6.32–6.28 (d, 1H, *J*=12.8 Hz), 5.96 (s, 1H), 3.12–3.09 (q, 2H, *J*=6.5 Hz), 1.51–1.49 (m, 2H), 1.25 (br, 18H), 0.90–0.85 (t, 3H, *J*=5.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 158.5, 151.9, 139.7, 133.7, 128.6, 128.5, 127.9, 12.3, 124.1, 121.4, 117.5, 101.3, 812, 49.4, 31.9, 31.0, 29.6, 29.6, 295, 29.2, 26.5, 22.7, 14.2. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{37}NO_2$: 420.2900 (M^+), found 420.2897.

*4.2.14. (Z)-2-Phenyl-3-[(phenylamino)methylene]chroman-4-one (**3n**).* Yellow solid, mp 101–104 °C. FTIR(film): ν_{max} 3053, 2960, 2919, 2858, 1649,1601, 1466, 1277, 1218, 1150, 1100, 1022, 801, 753, 695, 499 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.91 (d, 1H, *J*=12.0 Hz), 7.95 (dd, 1H, *J*=1.6, 7.8 Hz), 7.52–7.35 (m,6H), 7.28–7.23 (m, 2H), 7.08–6.84 (m, 6H), 6.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.2, 158.1, 141.2, 139., 138.0, 133.5, 128.7127.7, 126.8, 125.6, 122.7, 122.6, 120.7, 116.8, 115.2, 104.6, 80.3. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{17}NO_2$: 327.1259 (M^+), found 327.1262.

*4.2.15. (E)-3-[(Dipropylamino)methylene]-2-phenylchro-man-4-one (**3o**).* Yellow solid, mp 153–154 °C. FTIR(film): ν_{max} 3075, 3050, 3031, 2961, 2928, 2872, 1645, 1583, 1546, 1461, 1329, 1240, 1010, 759, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95(s, 1H), 7.88(dd, 1H, *J*=1.2, 7.5 Hz), 7.43(d, 2H, *J*=7.2 Hz), 7.28–7.19(m, 4H), 6.90–6.85(t, 1H, *J*=7.2 Hz), 6.79(d, 1H, *J*=7.5 Hz), 6.41(s, 1H), 3.15–3.09(m, 4H), 1.69–1.62(m, 4H), 0.98–0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0, 157.6, 148.4, 140.9, 133.7, 128.4, 128.1, 127.9, 127.0, 123.7, 121.2, 117.6, 99.7, 76.7, 22.6, 10.8. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}NO_2$: 336.1958(M^-), found 336.1954.

4.3. Typical procedure for the synthesis of benzopyranylpyrimidines

To a solution of **3a** (60 mg, 0.2 mmol) and benzamidine hydrochloride (**4a**, 93 mg, 0.6 mmol) in ethanol (2 mL) was added solid NaOH (16 mg, 0.4 mmol), followed by heating to 80 °C and stirring for 5 h. After cooling to room temperature, the crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=10:1) to give a white solid **5a** (57 mg, 85%).

*4.3.1. 5-Diphenyl-5H-chromeno[4,3-d]pyrimidine (**5a**).* White solid, mp 124–125 °C. FTIR(film): ν_{max} 1701, 1695, 1620, 1584, 1212, 850, 750, 721, 659 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.53–8.50 (m, 2H), 8.42–8.39 (dd, 1H, *J*=1.6, 7.8 Hz), 8.12 (s, 1H), 7.48–7.44 (m, 3H), 7.40–7.34 (m, 6H), 7.13–7.08 (m, 1H), 6.98–6.95 (d, 1H, *J*=8.1 Hz), 6.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 156.8, 155.3, 154.2, 138.0, 137.6, 133.6, 130.8, 129.2, 128.9, 128.6, 128.3, 127.8, 125.4, 123.2, 122.5, 121.1, 117.6, 77.9. HRMS (EI): *m*/*z* calcd for $C_{23}H_{16}N_2O$: 336.1263 (M^+), found 336.1266.

*4.3.2. 5-(4-Fluorophenyl)-2-phenyl-5H-chromeno[4,3-d]pyrimidine (**5b**).* White solid, mp 135–137 °C. FTIR(film): ν_{max} 1763, 1565, 1541, 1456, 1425, 738, 657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.57–8.54 (m, 2H), 8.47–8.44 (dd, 1H, *J*=1.6, 7.8 Hz), 8.18 (s, 1H), 7.52–7.50 (m, 3H), 7.45–7.43 (m, 3H), 7.20–7.08 (m, 3H), 7.02–6.99 (d, 1H, *J*=8.1 Hz), 6.32, (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 164.5, 161.5, 156.5, 155.3, 154.1, 137.5, 133.9, 133.7, 130.9, 129.8, 129.7, 128.6, 128.3, 125.4, 123.0, 122.6 (m), 121,1, 117.6, 116.1, 115.8, 77.2. HRMS (EI): *m*/*z* calcd for $C_{23}H_{15}FN_2O$: 354.1168 (M^+), found: 354.1165.

*4.3.3. 2-Phenyl-5-p-tolyl-5H-chromeno[4,3-d]pyrimidine (**5c**).* Yellow solid, mp 129–131 °C. FTIR(film): ν_{max} 1723, 1646, 1604, 1565, 1541, 1253, 1217, 1028, 892, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.57–8.54 (m, 2H), 8.47–8.43 (dd, 1H, *J*=1.6, 7.8 Hz), 8.20 (s, 1H), 7.51–7.49 (m, 3H), 7.45–7.39 (m, 1H), 7.34–7.32 (m, 2H), 7.25–7.23 (m, 1H), 7.20 (m, 2H), 7.18–7.12 (m, 1H), 7.02–6.99 (d, 1H, *J*=8.2 Hz), 6.32 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 156.8, 155.3, 154.2, 139.1, 137.6, 135.0, 133.6, 130.7, 129.6, 128.5, 128.2, 127.8, 125.4, 123.4, 122.4, 121.7, 117.7, 77.7, 21.2. HRMS (EI): *m*/*z* calcd for $C_{24}H_{18}N_2O$: 350.1419 (M^+), found: 350.1422.

Acknowledgements

We thank the National Natural Science Foundation of China, Ministry of Science and Technology (No. 2009ZX09501-006, 2007CB935900) and the Chinese Academy of Sciences for the financial support.

References and notes

1. For reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892; (b) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45–58; (c) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588; (d) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496–5514; (e) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674.
2. (a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48; (b) Masson, G.; Housseman, C.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628; (c) Shi, Y.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905–2916; (d) Shi, Y.-L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499–1504.
3. Azizi, N.; Saidi, M. R. *Tetrahedron Lett.* **2002**, *43*, 4305–4308.
4. For selected allylic amination of MBH adducts, see: (a) Kim, J.; Lee, H. J.; Gong, J. H. *Tetrahedron Lett.* **2002**, *43*, 9141–9146; (b) Du, Y.; Han, X.; Lu, X. *Tetrahedron Lett.* **2004**, *45*, 4967–4971; (c) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493–1499; (d) Cui, H. L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737–5740; (e) Pathak, R.; Madapa, S.; Batra, S. *Tetrahedron* **2007**, *63*, 451–460; (f) Cho, C. W.; Kong, J. R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337–1339; (g) Nag, S.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2007**, 911–917; (h) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927–930; (i) Singh, V.; Pathak, R.; Kartojiya, S.; Batra, S. *Synlett* **2005**, 2465–2468; (j) Phthak, R.; Batra, S. *Tetrahedron* **2007**, *6*, 9448–9455; (k) Nag, S.; Pathak, R.; Kumar, M.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3824–3828; (l) Rajesh, S.; Banerji, B.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 7852–7857; (m) Zhang, S. J.; Cui, H. L.; Jiang, K.; Li, R.; Ding, Z. Y.; Chen, Y. C. *Eur. J. Org. Chem.* **2009**, 5804–5809; (n) Wang, Y.; Shafiq, Z.; Liu, L.; Wang, D.; Chen, Y.-J. *J. Heterocycl. Chem.* **2010**, *47*, 373–378.
5. (a) Basavaian, D.; Rao, A. J. *Chem. Commun.* **2003**, 604–605; (b) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379–7382; (c) Schwartz, B. D.; Tilly, D. P.; Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2006**, 3181–3192; (d) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387–5391 For reviews see: (e) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (f) Rezgui, F.; Amri, H.; Gaï, M. M. E. *Tetrahedron* **2003**, *59*, 1369–1380; (g) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574 and references cited therein.
6. Shafig, Z.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2007**, *9*, 2525–2528.
7. Shafig, Z.; Qiao, Z.; Liu, L.; Zheng, Q.-Y.; Wang, D.; Chen, Y.-J. *Synlett* **2009**, 2965–2970.
8. Zhang, X. X.; Rao, W. D.; Chan, S. W. H.; Chan, P. W. H. *Org. Biomol. Chem.* **2009**, *7*, 4186–4193.
9. Liu, Y.-L.; Liu, L.; Wang, D.; Chen, Y.-J. *Tetrahedron* **2009**, *65*, 3473–3479.
10. Lee, K. Y.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2008**, *29*, 1099–1100.

11. (a) Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, *44*, 4365–4368; (b) Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, *47*, 73–77.
12. Stankovicova, H.; Lacova, M.; Gaplovsky, A.; Chovancova, J.; Pronayova, N. *Tetrahedron* **2001**, *57*, 3455–3464.
13. (a) Saari, W. S.; Wai, J. S.; Fisher, T. E.; Thomas, C. M.; Hoffman, J. M.; Rooney, C. S.; Smith, A. M.; Jones, J. H.; Bamberger, D. L.; Goldman, M. E.; O'brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Anderson, P. S. *J. Med. Chem.* **1992**, *35*, 3792–3802; (b) Gobbi, S.; Cavalli, A.; Rampa, A.; Belluti, F.; Piazzi, L.; Paluszcak, A.; Hartmann, R. W.; Recanatini, M.; Bisi, A. *J. Med. Chem.* **2006**, *49*, 4777–4780; (c) Wallen, E. A.; Dahlen, K.; Grotli, M.; Luthman, K. *Org. Lett.* **2007**, *9*, 389–391; (d) Luo, Y. P.; Yang, G. F. *Bioorg. Med. Chem.* **2007**, *15*, 1716–1724.
14. (a) Bruno, O.; Brullo, C.; Ranise, A.; Schenone, S.; Bondavalli, F.; Barocell, E.; Ballabeni, V.; Chiavarini, M.; Tognolini, M.; Impicciatore, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1397–1400; (b) Bruno, O.; Schenone, S.; Ranise, A.; Bondavalli, F.; Barocell, E.; Ballabeni, V.; Chiavarini, M.; Bartoni, S.; Tognolini, M.; Impicciatore, M. *Bioorg. Med. Chem.* **2001**, *9*, 629–636; (c) Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Ballabeni, V.; Barocell, E. *Bioorg. Med. Chem.* **2004**, *12*, 553–561; (d) An, H.; Eum, S.-J.; Koh, M.; Lee, S. K.; Park, S. B. *J. Org. Chem.* **2008**, *73*, 1752–1761.
15. CCDC 791851 contains the supplementary crystallographic data for **3f**. These data can be obtained free charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif, and are in the ESWI.
16. Wu, C.; Liu, Y.L.; Zeng, H.; Liu, L.; Wang, D.; Chen, Y. *J. Org. Biomol. Chem*., in press, doi:10.1039/c0ob00604a.
17. (a) Luo, S.; Wang, P. G.; Cheng, J. P. *J. Org. Chem.* **2004**, *69*, 555–558; (b) Luo, S.; Mi, X.; Wang, P. G.; Cheng, J. P. *J. Org. Chem.* **2004**, *69*, 8413–8422.