Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2539

www.rsc.org/obc

PAPER

First total synthesis of Papilistatin†

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Received 20th December 2010, Accepted 25th January 2011
DOI: 10.1039/c0ob01214a

Papilistatin has been isolated recently and found to have good anticancer and antibacterial activity. Papilistatin is a unique phenanthrene-1,10-dicarboxylic acid. The first total synthesis of papilistatin is described here with radical cyclisation as the key step.

Introduction

Papilistatin (Fig. 1) was isolated in 2010 by Pettit from a Taiwan butterfly, and was found to have anticancer and antibacterial activity.[1] Against a panel of six human and the murine P388 leukemia cancer cell lines, papilistatin exhibited cancer cell growth inhibition with GI_{50}'s of 0.093–3.5 μg mL^{-1}. We have been continuously studying the synthesis and biological activities of phenanthroindolizidine alkaloids.[2] Papilistatin is a unique phenanthrene-1,10-dicarboxylic acid which is similar to the intermediates used to construct phenanthroindolizidine alkaloids. Papilistatin's relatively simple structure and good biological activities evoked our interest. In order to explore if it can be used as an alternative to phenanthroindolizidine alkaloids, we developed the first total synthesis of papilistatin.

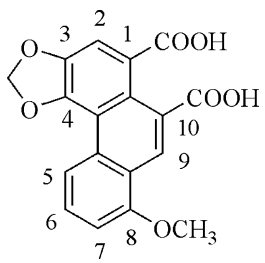
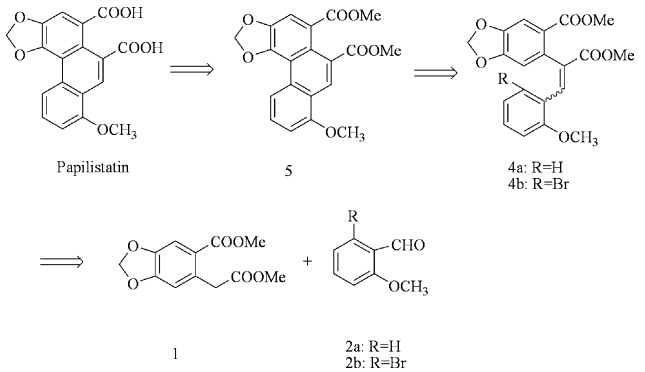


Fig. 1 Structure of papilistatin.

Results and discussion

Our retrosynthetic analysis is shown in Scheme 1. Apparently, the construction of the phenanthrene ring would be the key step to synthesize papilistatin. To the best of our knowledge, the most convenient way to construct the phenanthrene ring system is intramolecular oxidative coupling of diphenylethene using oxidative coupling reagents such as $Pb(OAc)_4$,[3] VOF_3,[4] $FeCl_3$,[2a,5] MnO_2,[6] and *m*-CPBA.[7] However, although we tried many oxidative coupling reagents (such as VOF_3, $FeCl_3$, MnO_2, *m*-CPBA and PIFA), no oxidative coupling product **5** was formed from **4a**. We believed that the electron-withdrawing methylcarbonyl group at the benzene ring of diphenylethene **4a** made the oxidative coupling impossible. We then introduced bromine into the compound **2a** to get **2b** and then to afford **4b**. An intramolecular coupling reaction of **4b** mediated by a palladium catalytic reaction was tried. But when we used $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ as the palladium catalyst, we also failed to construct the phenanthrene ring. Then we turned to radical cyclisation with Bu_3SnH and AIBN as reagents which were reported to be used to construct the phenanthrene ring system efficiently.[8] Using this method, we finally succeeded to get **5** from **4b**.



Scheme 1 Retrosynthetic analysis of papilistatin.

2-Methoxycarbonyl-4,5-methylenedioxyphenyl acetic acid methyl ester **1** was obtained employing piperonal **6** as the starting material. Condensation of commercially available piperonal **6** and malonic acid in the presence of piperidine and subsequent catalytic hydrogenation gave (3,4-methylenedioxy)phenylpropionic acid **8** in 74.8% yield over two steps.[9] **8** was treated with oxalyl choride in dichloromethane to give the corresponding acyl chloride, which formed 5,6-(methylenedioxy)-l-indanone **9** *via* intramolecular Friedel-Crafts acylation in the presence of $SnCl_4$ in 95% yield.[10] Treating indanone **9** with amyl nitrite in methanol with HC1 afforded the 2-(hydroxyimino)-5,6-(methylenedioxy)-1-indanon **10** in 75% yield.[10] Then treating the hydroxyimino ketone **10**

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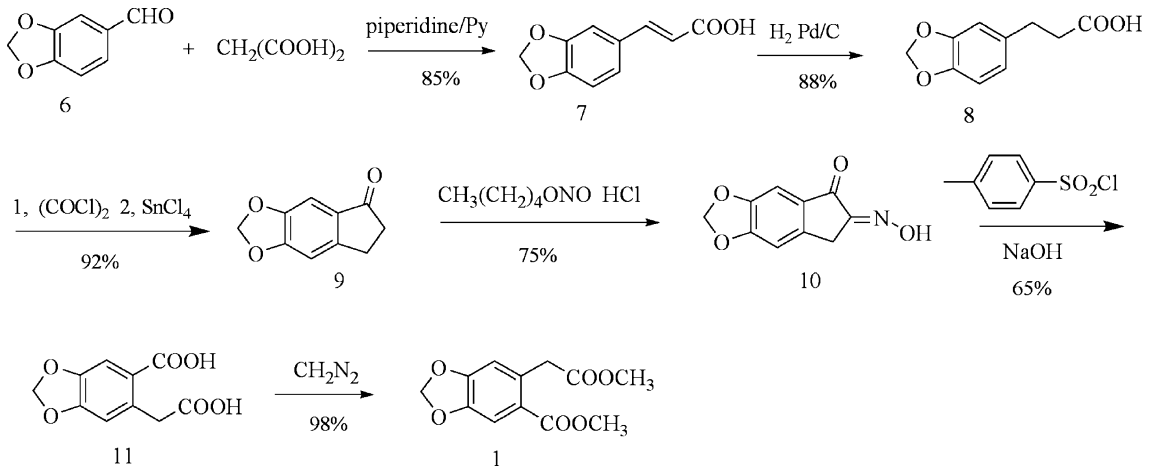
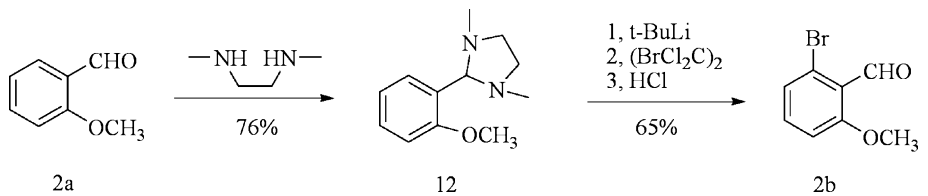
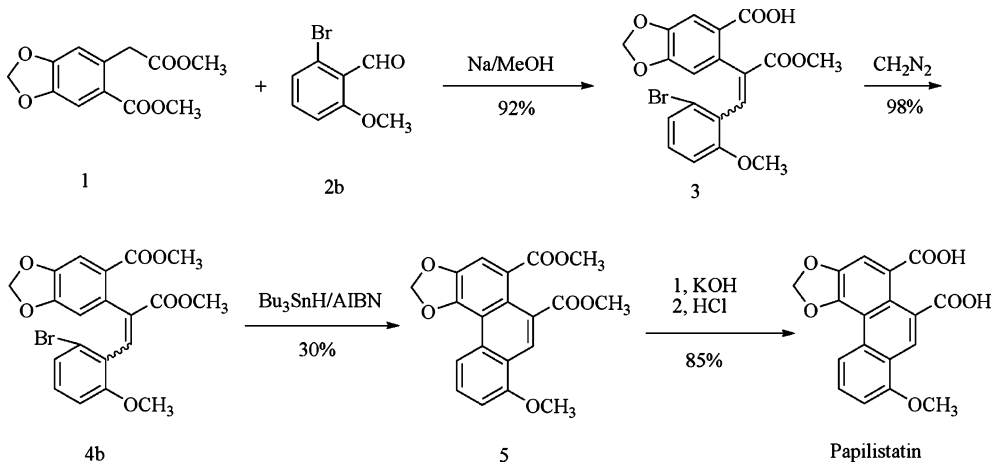
† Electronic Supplementary Information (ESI) available: 1H, ^{13}C-NMR and HRMS spectra for the compouds **1**, **3**, **4b**, **5**, **papilistatin**. See DOI: 10.1039/c0ob01214a.



Scheme 2 Synthesis of compound 1.



Scheme 3 Synthesis of compound 2.



Scheme 4 Synthesis of papilistatin.

with *p*-toluenesufonyl chloride in sodium hydroxide solution afforded 2-carboxy-4,5-methylenedioxyphenylacetic acid **11** *via* esterification, Beckmann rearrangement and subsequent hydrolysis in 65% yield.[11] Acid **11** reacted with diazomethane to give **1** in 98% yield (Scheme 2).

2-bromo-6-methoxybenzaldehyde **2b** could be easily synthesized from commercially available 2-methoxybenzaldehyde **2a** according to reported literature (Scheme 3).[12]

With **1** and **2b** in hand, we started to conduct reactions following our synthetic route (Scheme 4). The base-mediated condensation of aldehydes or ketones with dialkyl succinate to afford alkylidene succinic monoesters is known as Stobbe condensation. Stobbe condensation of **1** and **2b** in the presence of sodium methoxide in methanol afforded 3-(2-bromo-6-methoxyphenyl)-2-(2-carboxyl-4,5-methylenedioxyphenyl)-acrylic acid methyl ester **3** in a yield of 92% as a 1 : 1 mixture of *Z* and *E* isomers (as determined by ^{1}H NMR). Then **3** was treated with diazomethane to afford the corresponding dimethyl ester **4b** (*Z*/*E* = 1 : 1) in a yield of 98%. As we know, the *E* isomer of **4b** is more suitable than the *Z* isomer for intramolecular radical cyclisation, therefore we tried to improve the percentage of the *E* isomer in **3** and **4b**. But we found the percentage of the *E* isomer of **3** decreased when potassium *tert*-butoxide or sodium hydride was used as the base in Stobbe condensation. The effort to turn the *Z* isomers of **3** and **4b** to their corresponding *E* isomers also failed. The *Z* and *E* isomers of **3** and **4b** were very difficult to separate and only a little of the pure *Z* isomer of **4b** was obtained. Therefore, the mixture **4b** was used for the next step. As we got the pure *Z* isomer of **4b**, *Z* and *E* of **4b** can be easily assigned comparing their alkene-H chemical shift in NMR. According to the reference and chemdraw,

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the chemical shift of alkene-H in *E*-**4b** is more down-field than *Z*-**4b**, since in *E*-**4b** the ester group is at the *cis*-position of alkene-H, which can provide a greater deshielding effect. In the same way, we could assign the *Z* and *E* isomer of **3**. The intramolecular radical cyclisation of **4b** (*Z*/*E* = 1 : 1) with Bu_3SnH and AIBN proved to be a little complicated, and 3,4-methylenedioxy-8-methoxyphenanthrene-1,10-dicarboxylic acid dimethyl ester **5** was separated in a yield of 30%. The main by-product separated was **4a**. Treating the *Z* isomer of **4b** in the same condition could afford **5** only in 10%, which also accounted for the low yield of the reaction above. Nonetheless, **5** was obtained easily and then converted to its corresponding dicarboxylic acid **papilistatin** through saponification in a yield of 85%.

Conclusion

Papilistatin was first synthesized from easily available materials **1** and **2b** under mild conditions in only 4 steps with an overall yield of 23%. The chemistry described here provides a practical synthetic method of papilistatin, with which we could also prepare diversities of papilistatin for biochemical and pharmaceutical studies.

Experimental

The melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co, Beijing, China) and were uncorrected. ^{1}H NMR spectra were obtained by using a Bruker AV 400 spectrometer. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane.^{13}C NMR spectra were recorded by using a Bruker AV 400 (100 MHz) and $CDCl_3$, C_5D_5N or DMSO-d_6 as a solvent. Chemical shifts (δ) are reported in parts per million using the solvent peak. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). All anhydrous solvents were dried and purified by standard techniques just before use.

2-Methoxycarbonyl-4,5-methylenedioxyphenylacetic acid methyl ester (1)

Compound **11** (1.81 g, 8.10 mmol) in dry dichloromethane (15 mL) was cooled to 0 °C and then carefully treated with diazomethane until the reaction had finished. The excess diazomethane was decomposed with a few drops of glacial acetic acid. The resulting mixture was evaporated to afford 2.00 g (98%) of **1** as a white solid. mp 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1 H, Ph-H), 6.71 (s, 1 H, Ph-H), 6.03 (s, 2 H, OCH_2O), 3.93 (s, 2 H, Ph-CH_2-), 3.83 (s, 3 H, $COOCH_3$), 3.70 (s, 3 H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.6, 150.8, 146.8, 132,3, 122.7, 112.1, 110.7, 101.9, 51.9, 40.4. HRMS (ESI): calcd. for $C_{12}H_{12}O_6$ $[M + Na]^+$ 275.0526, found 275.0527.

(*Z*/*E*)-3-(2-Bromo-6-methoxyphenyl)-2-(2-carboxyl-4,5-methylenedioxyphenyl)-acrylic acid methyl ester (3)

Sodium (0.19 g, 8.10 mmol) was stirred in methanol (80 mL) until it disappeared. **1** (2.00 g, 7.94 mmol) and **2b** (1.73 g, 8.10 mmol) were added to the solution. The mixture was heated at reflux for 4 h and then rotary evaporated to remove most of the methanol. The resulting mixture was cooled to 0 °C and acidified with 2 mol L^{-1} hydrochloric acid, then filtered, washed with water and dried to give 3.17 g (92%) of **3** (*Z*/*E* = 1 : 1) as a white solid. mp 176–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1 H, C═CH), 7.56 (s, 1 H, C═CH), 7.55 (s, 1 H, Ar–H), 7.22 (d, *J* = 8.0 Hz, 1 H, Ar–H), 7.12–7.17 (m, 2 H, Ar–H), 7.06 (t, *J* = 8.0 Hz, 1 H, Ar–H), 7.02 (s, 1 H, Ar–H), 6.86 (d, *J* = 8.0 Hz, 1 H, Ar–H), 6.75 (s, 1 H, Ar–H), 6.62 (d, *J* = 8.4 Hz, 1 H, Ar–H), 6.42 (s, 1 H, Ar–H), 6.11 (s, 2 H, OCH_2O), 5.97 (s, 2 H, OCH_2O), 3.80 (s, 6 H, $COOCH_3$), 3.51 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.5, 167.1, 166.3, 157.8, 156.9, 147.5, 147.1, 137.8, 137.5, 135.0, 134.2, 133.9, 130.0, 129.4, 126.9, 125.2, 124.4, 124.3, 123.6, 122.0, 112.3, 110.7, 110.6, 109.5, 102.2, 101.9, 56.0, 55.2, 52.2, 51.4. HRMS (ESI): calcd. for $C_{19}H_{15}BrO_7$ $[M - H]^-$ 432.9928, found 432.9922.

(*Z*/*E*)-3-(2-Bromo-6-methoxyphenyl)-2-(2-methoxycarbonyl-4,5-methylenedioxyphenyl)-acrylic acid methyl ester (4b)

Compound **3** (3.17 g, 7.30 mmol) was dissolved in dry dichloromethane (40 mL) and cooled to 0 °C and then carefully treated with diazomethane until the reaction had finished. The excess diazomethane was decomposed with a few drops of glacial acetic acid. The resulting mixture was evaporated to afford 3.31 g (98%) of **4b** as a white oil. A little of the *Z* isomer of **4b** could be obtained through column chromatography (petroleum ether–EtOAc, 8 : 1, v/v). For **4b** (*Z*/*E* = 1 : 1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1 H, C═CH), 7.48 (s, 1 H, C═CH), 7.46 (s, 1 H, Ar–H), 7.20 (d, *J* = 8.0 Hz, 1 H, Ar–H), 7.12 (t, *J* = 8.8 Hz, 1 H, Ar–H), 7.11 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.02 (t, *J* = 8.0 Hz, 1 H, Ar–H), 6.98 (s, 1 H, Ar–H), 6.84 (d, *J* = 8.0 Hz, 1 H, Ar–H), 6.69 (s, 1 H, Ar–H), 6.59 (d, *J* = 8.4 Hz, 1 H, Ar–H), 6.38 (s, 1 H, Ar–H), 6.06 (s, 2 H, OCH_2O), 5.92 (s, 2 H, OCH_2O), 3.84 (s, 3 H, $COOCH_3$), 3.79 (s, 6 H, $COOCH_3$), 3.78 (s, 3 H, $COOCH_3$), 3.52 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3); For the *Z* isomer of **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1 H, C═CH), 7.20 (d, *J* = 8.0 Hz, 1 H, Ar–H), 7.13 (t, *J* = 8.0 Hz, 1 H, Ar–H), 6.99 (s, 1 H, Ar–H), 6.84 (d, *J* = 8.0 Hz, 1 H, Ar–H), 6.69 (s, 1 H, Ar–H), 6.07 (s, 2 H, OCH_2O), 3.79 (s, 3 H, $COOCH_3$), 3.78 (s, 3 H, $COOCH_3$), 3.52 (s, 3 H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.0, 156.9, 150.2, 147.0, 137.8, 133.9, 133.7, 130.0, 125.1, 124.3, 124.2, 122.9, 110.4, 109.9, 109.5, 101.9, 55.1, 52.1, 51.8. HRMS (ESI): calcd. for $C_{20}H_{17}BrO_7$ $[M + Na]^+$ 471.0050, found 471.0052.

3,4-Methylenedioxy-8-methoxyphenanthrene-1,10-dicarboxylic acid dimethyl ester (5)

To a solution of **4b** (3.31 g, 7.16 mmol) in toluene (200 mL), AIBN (0.23 mg, 1.43 mmol) and Bu_3SnH (5.00 g, 17.18 mmol) were added, and the mixture was heated under reflux for 6 h. The reaction mixture was concentrated by rotary evaporation, and purified by column chromatography (petroleum ether–EtOAc, 10 : 1, v/v) to give 0.82 g (30%) of **5** as a yellow solid. mp 212–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 8.0 Hz, 1 H, H-5), 8.67 (s, 1 H, H-9), 7.71 (s, 1 H, H-2), 7.63 (t, *J* = 8.0 Hz, 1 H, H-6), 7.06 (d, *J* = 8.0 Hz, 1 H, H-7), 6.32 (s, 2 H, OCH_2O), 4.04 (s, 3 H, OCH_3), 3.92 (s, 3 H, $COOCH_3$), 3.90 (s, 3 H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.8, 156.1, 146.6, 144.9,

130.4, 129.2, 127.2, 125.4, 124.2, 123.8, 121.2, 119.0, 117.8, 112.1, 107.3, 101.9, 55.7, 52.1, 52.0. HRMS (ESI): calcd. for $C_{20}H_{16}O_7$ $[M + Na]^+$ 391.0788, found 391.0796.

Papilistatin

Compound **5** (0.82 g, 2.15 mmol) was dissolved in methanol (35 mL) and dioxane (30 mL) and then 20% potassium hydroxide (55 mL) was added to the solution. The mixture was warm to 40 °C and stirred for 6 h. The mixture was rotary evaporated to remove dioxane and methanol, and the resulting mixture was cooled to 0 °C and acidified with 2 mol L^{-1} hydrochloric acid to afford 0.62 g (85%) of papilistatin as a yellow solid. mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (br, 1 H, COOH), 12.85 (br, 1 H, COOH), 8.65 (d, J = 8.4 Hz, 1 H, H-5), 8.45 (s, 1 H, H-9), 7.74 (t, J = 8.4 Hz, 1 H, H-6), 7.70 (s, 1 H, H-2), 7.30 (d, J = 8.0 Hz, 1 H, H-7), 6.44 (s, 2 H, OCH_2O), 4.04 (s, 3 H, OCH_3); ^{1}H NMR (400 MHz, C_5D_5N) δ 9.29 (s, 1 H, H-9), 8.84 (d, J = 8.0 Hz, 1 H, H-5), 8.21 (s, 1H, H-2), 7.67 (t, J = 8.0 Hz, 1 H, H-6), 7.08 (d, J = 8.0 Hz, 1 H, H-7), 6.23 (s, 2 H, OCH_2O), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (100 MHz, C_5D_5N) δ 172.2, 171.7, 156.8, 146.7, 145.8, 131.9, 131.2, 129.6, 129.0, 125.3, 124.7, 122.3, 120.1, 118.8, 112.8, 108.3, 102.8, 56.2. HRMS (ESI): calcd. for $C_{18}H_{12}O_7$ $[M - H]^-$ 339.0510, found 339.0501.

Acknowledgements

We are grateful to the National Key Project for Basic Research (2010CB126100) and the National Natural Science Foundation of China (20872072) for generous financial support for our programs.

Notes and references

1 G. R. Pettit, Q. H. Ye, D. L. Herald, F. Hogan and R. K. Pettit, *J. Nat. Prod.*, 2010, **73**, 164–166.
2 (*a*) K. L. Wang, M. Y. Lü, Q. M. Wang and R. Q. Huang, *Tetrahedron*, 2008, **64**, 7504–7510; (*b*) Z. W. Wang, Z. Li, K. L. Wang and Q. M. Wang, *Eur. J. Org. Chem.*, 2010, 292–299; (*c*) M. B. Cui, H. J. Song, A. Z. Feng, Z. W. Wang and Q. M. Wang, *J. Org. Chem.*, 2010, **75**, 7018–7021; (*d*) K. L. Wang, B. Su, Z. W. Wang, M. Wu, Z. Li, Y. N. Hu, Z. J. Fan, N. Mi and Q. M. Wang, *J. Agric. Food Chem.*, 2010, **58**, 2703–2709; (*e*) K. L. Wang, Y. N. Hu, Y. X. Liu, N. Mi, Z. J. Fan, Y. Liu and Q. M. Wang, *J. Agric. Food Chem.*, 2010, **58**, 12337–12342.
3 K. S. Feldman and S. M. Ensel, *J. Am. Chem. Soc.*, 1994, **116**, 3357–3366.
4 (*a*) B. Halton, A. I. Maidment, D. L. Officer and J. M. Warner, *Aust. J. Chem.*, 1984, **37**, 2119–2128; (*b*) D. A. Evans, C. J. Dinsmore, D. A. Evrard and K. M. DcVries, *J. Am. Chem. Soc.*, 1993, **115**, 6426–6427; (*c*) A. Furstner and J. W. J. Kennedy, *Chem.–Eur. J.*, 2006, **12**, 7398–7410.
5 K. L. Wang, M. Y. Lü, A. Yu, X. Q. Zhu and Q. M. Wang, *J. Org. Chem.*, 2009, **74**, 935–938.
6 K. L. Wang, Y. N. Hu, Z. Li, M. Wu, Z. H. Liu, B. Su, A. Yu, Y. Liu and Q. M. Wang, *Synthesis*, 2009, **7**, 1083–1090.
7 K. L. Wang, Y. N. Hu, M. Wu, Z. Li, Z. H. Liu, B. Su, A. Yu, Y. X. Liu and Q. M. Wang, *Tetrahedron*, 2010, **66**, 9135–9140.
8 (*a*) D. C. Harrowven, M. I. T. Nunn and D. R. Fenwick, *Tetrahedron Lett.*, 2002, **43**, 3185–3187; (*b*) D. C. Harrowven, I. L. Guy and L. Nanson, *Angew. Chem., Int. Ed.*, 2006, **45**, 2242–2245; (*c*) H. Suzuki, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 1996, **60**, 6114–6122; (*d*) A. Couture, E. Deniau, P. Grandclaudon and C. Hoarau, *J. Org. Chem.*, 1998, **63**, 3128–3132.
9 H. Yasushi, O. Momotoshi and S. Yoshihiro, *Biosci., Biotechnol., Biochem.*, 2003, **67**, 2183–2193.
10 E. N. David, K. B. William, P. J. Michael, O. Robert and M. R. Robert, *J. Med. Chem.*, 1990, **33**, 703–710.
11 N. J. Srivastava and D. N. Chaudhury, *J. Org. Chem.*, 1962, 4337–4341.
12 M. Rawat, V. Prutyanov and W. D. Wulff, *J. Am. Chem. Soc.*, 2006, **128**, 11044–11053.

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