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Single-step synthesis of idebenone from Coenzyme Q_0 via free-radical alkylation under silver catalysis

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ABSTRACT

Idebenone was synthesized directly by free-radical alkylation of 2,3-dimethyl-1,4-benzoquinone (Coenzyme Q_0) with commercially available 11-hydroxyundecanoic acid in the presence of potassium peroxodisulfate and silver nitrate in a mixed solvent (CH_3CN–H_2O, 1:1) under mild condition in good yields (65%, based on Coenzyme Q_0). The reaction is operationally simple and could be used in the preparation of other biologically Coenzyme Q analogues.

1. Introduction

Idebenone (2,3-Dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone, Fig. 1) is a synthetic analog of Coenzyme Q_{10}, a free radical scavenger for reactive oxygen species (ROS) and facilitating electron transfer along the mitochondrial respiratory chain.[1] It has been widely used in the treatment of neurodegenerative and mitochondrial disorders, such as Alzheimer's disease, Parkinson's disease, Friedreich's ataxia, etc.[2] In comparison with Coenzyme Q_{10} (C40 side chain), idebenone (C10 side chain) has a shorter carbon chain that facilitates interception of free radicals both in hydrophobic and hydrophilic environments. Theoretically, idebenone may posses greater bioavailability than Coenzyme Q_{10} due to its decreased molecular weight and increased water solubility.[3] More recently, idebenone has been recommended as a potential treatment for Leber's hereditary optic neuropathy (LHON) and Duchenne muscular dystrophy (DMD).[4]

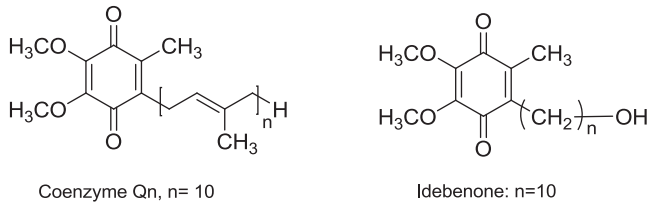

Fig. 1. Coenzyme Q_{10} and idebenone.

To date, methods for the synthesis of idebenone are limited, few synthetic processed to idebenone have been disclosed.[5] The major divergence of theses processes were the starting materials, either Friedel–Crafts acylation of 3,4,5-trimethoxytoluene (or 2,3,4,5-tetramethoxytoluene, 16% total yield),[5a,b] [Scheme 1, (**1**)] or Heck coupling reaction of 2-bromo-3,4,5-trimethoxytoluene (20% total yield)[5c] [Scheme 1, (**2**)]. However, both methods involve multistep procedures under harsh reaction conditions, in which toxic reagents or metallic catalysts [NaCN, $KMnO_4$, PtO_2, $Pd(AcO)_2$, etc.] are often used.[5] Therefore, a convenient and practical synthetic route for the preparation of idebenone is highly demanded.

In recent years, transition-metal-catalyzed decarboxylative cross-coupling reactions using carboxylic acids as coupling partners have been widely studied in organic synthesis as novel methods for the formation of carbon–carbon bonds.[6] The Minisci reactions, which involving the addition of radicals to heteroaromatic base under $AgNO_3$ catalysis are valuable C–H functionalization processes within medicinal chemistry.[7] Although the Minisci reaction is useful in coupling nitrogen-containing heterocyclic compounds with aldehydes, carboxylic acids, and boronic acids, it is associated with a few limitations.[6,7] Radicals generated

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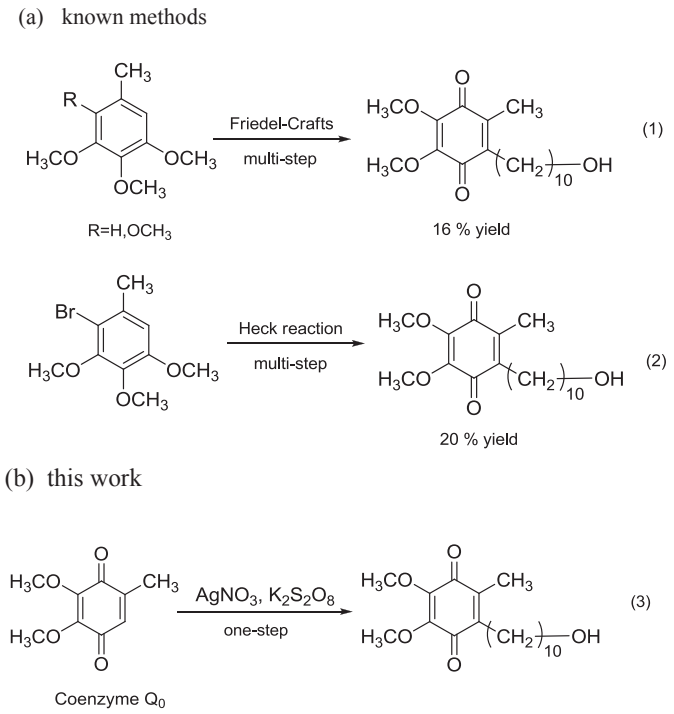
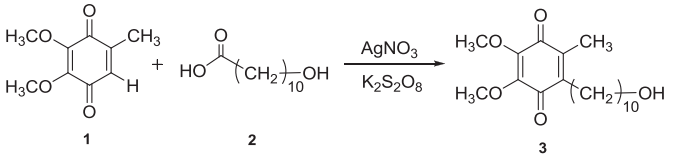


Scheme 1. Various approaches for idebenone.

by decarboxylaion of carboxylic acids with $K_2S_2O_8$ and $AgNO_3$ could be used for the alkylation of quinones was reported by Liu et al.[6b] and Fausta et al.,[6c] however, to the best of our knowledge, practical C–H functionalization of Coenzyme Q_0 with long chain carboxylic acids were few reported,[6d–h] which would provide a novel C–C cross-coupling method of idebenone. Following our recent work on synthesis of Coenzyme Q analogues,[8] herein we describe a one-step synthesis of idebenone by alkylation of Coenzyme Q_0 **1** with commercially available 11-hydroxyundecanoic acid **2** through direct decarboxylative cross-coupling reaction under silver catalysis [Scheme 1, (**3**)].

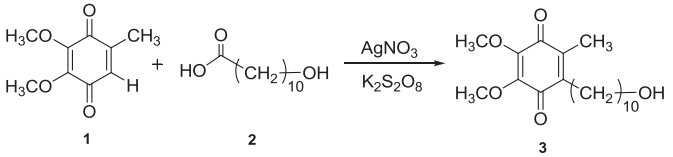
2. Results and discussion

We began our studies with the commercially available Coenzyme Q_0 **1** and 11-hydroxyundecanoic acid **2** (Scheme 2). 11-hydroxyundecanoic acid **2** was selected because it is monocarboxylic acid and it could generate the 10 carbon alkyl radical in the presence of silver (I) and peroxodisulfate, which may facilitate addition to the C-6 position of Coenzyme Q_0 to form idebenone. When 1 equiv of Coenzyme Q_0 **1** was treated with **2** in the presence of 0.1 equiv of $AgNO_3$ and 1.5 equiv of $K_2S_2O_8$ in CH_3CN–H_2O (v/v=1:1) at 75 °C, we were delighted to know that our desired idebenone **3** was indeed formed in 34% yield (Table 1, entry 1). The control experiment showed that a silver catalyst was necessary for this reaction to proceed (Table 1, entry 2). Then, several other silver catalysts were screened in the reaction, Ag_2CO_3, AgOAc and Ag_2O catalyzed the reaction with moderate efficiency (Table 1, entries 3–5), and $AgNO_3$ was ultimately chosen as the catalyst because it formed idebenone in the best yield and is less expensive than other silver catalysts. Other oxidants, such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$,[5e,6e–g] H_2O_2 and TBHP were also examined in the reaction, unfortunately, only $Na_2S_2O_8$ can catalyze this reaction with a moderate yield (30%) (Table 1, entries 6–9). It is necessary to note that the methodology to prepare idebenone reported previously in a patent from 1996 by Morimasa[5e] utilizing $(NH_4)_2S_2O_8$ gives the desired product in 88.8% yield, which is quite doubtful. Then, the effect of the amount of 11-hydroxyundecanoic acid **2**, $AgNO_3$ and $K_2S_2O_8$ was examined, and the results showed that an increase in the amount of $AgNO_3$ and $K_2S_2O_8$ lead to higher conversion of Coenzyme Q_0. When we used 1.3 equiv of **2**, 0.3 equiv of $AgNO_3$ and 2 equiv of $K_2S_2O_8$, we obtained the highest yield (65%) of idebenone **3** (Table 1, entries 10–13). Solvents were crucial for this reaction, using THF-H_2O, Acetone-H_2O, DMF-H_2O or CH_2Cl_2–H_2O as solvent led to a trace amount of idebenone **3** (Table 1, entries 14–17). Further screening of the reaction time showed that 3 h was the best choice. On the basis of these screening studies, the optimal condition was using 11-hydroxyundecanoic acid **2** (1.3 equiv), $AgNO_3$ (0.3 equiv), and $K_2S_2O_8$ (2 equiv) in the mixed solvent of CH_3CN–H_2O (v/v=1:1) at 75 °C for 3 h (Table 1, entry 11).



Scheme 2. Single-step synthesis of idebenone from Coenzyme Q_0 via free-radical alkylation.

Table 1
Optimization studies of silver-catalyzed free-radical alkylation of Coenzyme Q_0[a]

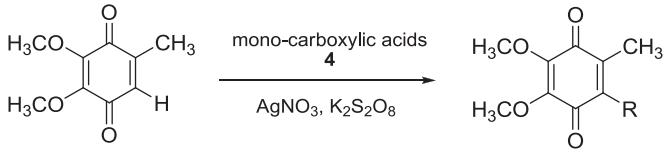


Entry	Catalyst (equiv.)	Oxidant (equiv.)	Mixed solvent	Yield[b] (%)
1	$AgNO_3$ (0.1)	$K_2S_2O_8$ (1.5)	CH_3CN–H_2O	34
2[c]		$K_2S_2O_8$ (1.5)	CH_3CN–H_2O	0
3	Ag_2CO_3 (0.1)	$K_2S_2O_8$ (1.5)	CH_3CN–H_2O	22
4	AgOAc (0.1)	$K_2S_2O_8$ (1.5)	CH_3CN–H_2O	25
5	Ag_2O (0.1)	$K_2S_2O_8$ (1.5)	CH_3CN–H_2O	18
6	$AgNO_3$ (0.1)	$Na_2S_2O_8$ (1.5)	CH_3CN–H_2O	30
7	$AgNO_3$ (0.1)	$(NH_4)_2S_2O_8$ (2)	CH_3CN–H_2O	Trace
8	$AgNO_3$ (0.1)	H_2O_2 (2)	CH_3CN–H_2O	0
9	$AgNO_3$ (0.1)	TBHP (2)	CH_3CN–H_2O	0
10	$AgNO_3$ (0.2)	$K_2S_2O_8$ (2)	CH_3CN–H_2O	44
11	**$AgNO_3$ (0.3)**	**$K_2S_2O_8$ (2)**	**CH_3CN–H_2O**	**65**
12[d]	$AgNO_3$ (0.4)	$K_2S_2O_8$ (3)	CH_3CN–H_2O	62
13[d]	$AgNO_3$ (0.5)	$K_2S_2O_8$ (4)	CH_3CN–H_2O	60
14	$AgNO_3$ (0.3)	$K_2S_2O_8$ (2)	THF-H_2O	Trace
15	$AgNO_3$ (0.3)	$K_2S_2O_8$ (2)	Acetone-H_2O	Trace
16	$AgNO_3$ (0.3)	$K_2S_2O_8$ (2)	DMF-H_2O	0
17	$AgNO_3$ (0.3)	$K_2S_2O_8$ (2)	CH_2Cl_2–H_2O	0

[a] Reaction Conditions: **1** (6 mmol), **2** (1.3 equiv), catalyst, oxidant and 80 mL of mixed solvent (v/v=1:1).
[b] Yield of pure isolated products.
[c] No $AgNO_3$ added.
[d] 1.5 equiv of **2** added.

With the optimized conditions, some commercially available short chain mono-carboxylic acids **4** were investigated in this free-radical decarboxylative cross-coupling reaction and the results were summarized in Table 2. The free-radical alkylation proceeded smoothly in the presence of $AgNO_3$ and $K_2S_2O_8$ in the mixed solvent of CH_3CN–H_2O at 75 °C, mono-carboxylic acids: glycolic acid **4a**, chloroacetic acid **4b**, methoxyacetic acid **4c**, ethoxyacetic acid **4d** all direct C-6 alkylation with Coenzyme Q_0 **1** to form the corresponding Coenzyme Q analogues **5** (Table 2, entries 1–4).

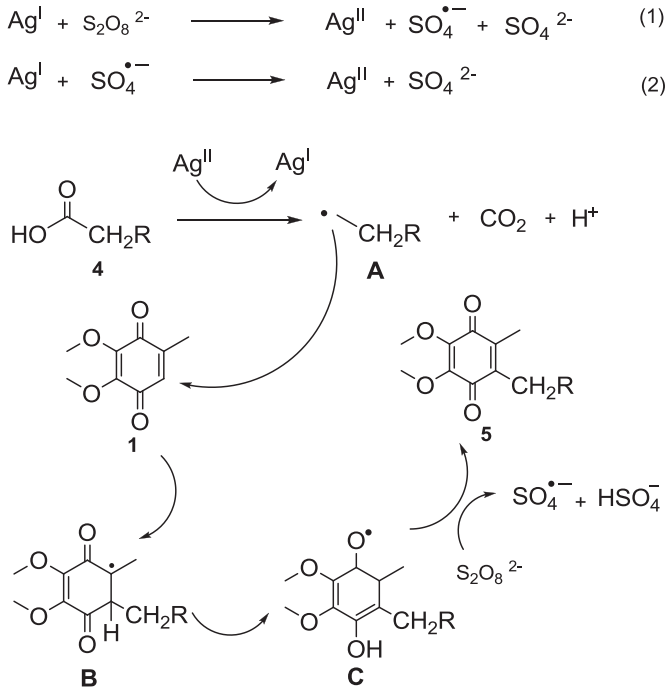
Table 2
Free-radical alkylation of Coenzyme Q_0 **1** with different mono-carboxylic acids **4**[a]



Entry	4	R	5	Yield[b] (%)
1	4a	CH_2OH	5a	20
2	4b	CH_2Cl	5b	18
3	4c	CH_2OCH_3	5c	32
4	4d	$CH_2OCH_2CH_3$	5d	35

[a] Reaction Conditions: **1** (6 mmol), **4** (1.3 equiv), $AgNO_3$ (0.3 equiv), and $K_2S_2O_8$ (2 equiv) and 80 mL of mixed solvent (v/v=1:1).
[b] Yield of pure isolated products.

On the basis of the literature precedence,[6,7,9] we assumed that the reaction is proceeding through a radical mechanism as shown in Scheme 3. Initially, an Ag(I) cation is oxidized to an Ag(II) cation by peroxodisulfate [Eq. (1)] and a sulfate radical ion ($SO_4^{\bullet-}$) [Eq. (2)]. Then, mono-carboxylic acids **4** reacted with the Ag(II) cation to form alkyl radical (A) by losing a proton, one molecule of CO_2 and the Ag(I) cation. The obtained radical (A) subsequently underwent hydrogen atom abstraction from the C-6 position of Coenzyme Q_0 **1** forming a coupling intermediate (B), which can transfer to the hydroquinol radical (C), subsequently the hydroquinol radical (C) is oxidized to Coenzyme Q **5** by peroxodisulfate.



Scheme 3. Proposed mechanism for the silver-catalyzed decarboxylative cross-coupling reaction for the synthesis of Coenzyme Q analogues.

3. Conclusion

In summary, a silver-catalyzed free-radical direct C-6 alkylation of Coenzyme Q_0 **1** with commercially available 11-hydroxyundecanoic acid **2** for the preparation of idebenone **3** has been developed, the reaction is clean without by-products and a 65% yield is quite respectable for such a reaction. This protocol provided a new avenue to form C–C bonds between Coenzyme Q_0 and carboxylic acids for the preparation of Coenzyme Q analogues **5**. The reaction was performed at 75 °C with no requirement of strict water- and oxygen-free conditions, and is amenable to the gram-scale synthesis of idebenone. Therefore, this synthetic method would have potential industrial application in the preparation of idebenone and other biologically Coenzyme Q analogues.

4. Experimental section

4.1. General

The synthesized CoQ analogues were purified by silica gel (80–100 mesh) column chromatography (Adamas-beta, China) and identified by thin-layer chromatography (TLC), MS, and NMR analysis. The melting points were measured with an YRT-3 temp apparatus and are uncorrected. ^1H NMR spectra and ^{13}C NMR were recorded on a Bruker DRX NMR spectrometer, respectively, Mass spectra were obtained on a ZAB-2F mass spectrometer. Potassium persulfate ($K_2S_2O_8$) and silver nitrate ($AgNO_3$) were purchased from Adamas-beta, China. Coenzyme Q_0 **1**, 11-hydroxyundecanoic acid **2** and mono-carboxylic acids **4** were purchased from Adamas-beta and Sigma–Aldrich. Other chemicals used were of analytical grade.

4.2. General procedure for synthesis of idebenone 3 and Coenzyme Q analogues 5

To a solution of Coenzyme Q_0 **1** (1.09 g, 6 mmol) and 11-mono-carboxylic acids **2** or **4** (7.8 mmol) in acetonitrile 40 mL and distilled water 10 mL was added $AgNO_3$ (0.31 g, 1.8 mmol). The mixture was heated to 75 °C and a solution of $K_2S_2O_8$ (3.24 g, 12 mmol) in distilled water 30 mL was added dropwise over 2 h, then the reaction mixture was stirred for another 1 h. The resulting mixture was cooled and extracted with CH_2Cl_2 and the organic layer was washed with water, then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by short column chromatograph on silica gel (eluent: PE/EtOAc=3:1 or 5:1) to give idebenone **3** or Coenzyme Q analogues **5**.

4.2.1. Idebenone ***3***. (1.32 g, 65%), yellow needles, mp 53–55 °C (Lit[5a] 55.5 °C). ^1H NMR (400 MHz, $CDCl_3$): 4.01 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.66 (t, 2H, *J*=6.4 Hz, CH_2OH), 2.47 (t, 2H, *J*=6.8 Hz, CH_2-CoQ_0), 2.03 (s, 3H, CH_3), 1.65–1.53 (m, 2H), 1.46–1.24 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): 184.7 (C=O), 184.2 (C=O), 144.3, 143.1 (2C), 138.7, 63.1 (**C**H_2OH), 61.1 (O**C**H_3), 32.8, 29.8, 29.5, 29.4, 29.3, 28.7, 26.4 and 25.7 (CH_2-side chain), 11.9 (**C**H_3).

4.2.2. Compound ***5a***. (0.25 g, 20%), orange solid, mp 50–51 °C (Lit[5g] 53–55 °C). ^1H NMR (500 MHz, $CDCl_3$): 4.45 (s, 2H, CH_2OH), 3.92 (s, 6H, OCH_3), 2.92 (s, 1H, OH), 2.02 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 184.9 (C=O), 184.5 (C=O), 144.6, 144.1, 140.6, 138.6, 61.1 (O**C**H_3), 56.5 (**C**H_2OH), 11.6 (**C**H_3).

4.2.3. Compound ***5b***.[8c] (0.24 g, 18%), orange oil, ^1H NMR (500 MHz, $CDCl_3$): 4.29 (s, 2H, CH_2Cl), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, MeOD):183.7 (C=O), 181.6 (C=O), 144.7, 144.2, 142.3, 136.7, 61.2 (O**C**H_3), 61.1 (O**C**H_3), 35.0 (**C**H_2Cl), 11.8 (**C**H_3); MS (ESI): *m*/*z*=231 (M^++H).

4.2.4. Compound ***5c***. (0.43 g, 32%), orange solid, mp 33–34 °C (Lit[5g] 36 °C); ^1H NMR (500 MHz, D_2O): 4.18 (s, 2H, C**H**$_2$OCH$_3$), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.24 (s, 3H, CH_2OC**H**$_3$), 1.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, MeOD):184.3(C=O), 183.2(C=O), 144.4, 144.2, 143.0, 136.5, 64.0(**C**H_2OCH_3), 61.0 (O**C**H_3), 58.6 (O**C**H_3),

11.9($CH_2O\mathbf{C}H_3$); HRMS-ESI: m/z (M^--H) Calcd for $C_{11}H_{13}O_5$: 225.0762. Found: 225.0759.

*4.2.5. Compound **5d**.* (0.50 g, 35%), orange oil, ^1H NMR (400 MHz, $CDCl_3$): 4.30 (s, 2H, $C\mathbf{H_2}OCH_2CH_3$), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.50 (q, J=7.1 Hz, 2H, $CH_2OC\mathbf{H_2}CH_3$), 2.07 (s, 3H, CH_3), 1.19–1.16 (t, J=7.1 Hz, 3H, $CH_2OCH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): 184.5(C=O), 183.3(C=O), 144.5, 144.4, 143.1, 136.9, 66.6 ($\mathbf{C}H_2OCH_2CH_3$), 62.2($CH_2O\mathbf{C}H_2CH_3$), 61.1($O\mathbf{C}H_3$), 61.1($O\mathbf{C}H_3$), 15.1(CH_3), 12.0($CH_2OCH_2\mathbf{C}H_3$); HRMS-ESI: m/z (M^++Na) Calcd for $C_{12}H_{16}O_5Na$: 263.0895. Found: 263.0892.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.10.017.

References and notes

1. (a) Imre, Z.-M. *Arch. Gerontol. Geriatr.* **1990**, *11*, 177; (b) Mordente, A.; Martorana, G. E.; Minotti, G.; Giardina, B. *Chem. Res. Toxicol.* **1998**, *11*, 54; (c) Giorgio, V.; Petronilli, V.; Ghelli, A.; Carelli, V.; Rugolo, M.; Lenaz, G.; Bernardi, P. *Biochim. Biophys. Acta* **2012**, *1817*, 363.
2. (a) Liu, J.; Wang, L. N. *CNS Drugs.* **2014**, *28*, 63; (b) Mancuso, M.; Orsucci, D.; Volpi, L.; Calsolaro, V.; Siciliano, G. *Curr. Drug. Targets* **2010**, *11*, 111; (c) Arpa, J.; Sanz-Gallego, I.; Rodríguez-de-Rivera, F. J.; Domínguez-Melcón, F. J.; Prefasi, D.; Oliva-Navarro, J.; Moreno-Yangüela, M. *Acta. Neurol. Scand.* **2014**, *129*, 32; (d) Kerr, D. S. *Neurotherapeutics* **2013**, *10*, 307; (e) Mecocci, P.; Polidori, M. C. *Biochim. Biophys. Acta* **2012**, *1822*, 631.
3. Parkinson, M. H.; Schulz, J. B.; Giunti, P. *J. Neurochem.* **2013**, *126*, 125.
4. (a) Hargreaves, I. P. *Int. J. Biochem. Cell Biol.* **2014**, *49*, 105; (b) Buyse, G. M.; Goemans, N.; van den Hauwe, M.; Thijs, D.; de Groot, I. J.; Schara, U.; Ceulemans, B.; Meier, T.; Mertens, L. *Neuromuscul. Disord.* **2011**, *21*, 396.
5. (a) Goto, G.; Okamoto, K.; Okutani, T.; Isuke, I. *Chem. Pharm. Bull.* **1985**, *33*, 4422; (b) Lu, L.; Chen, F. *Synth. Commun.* **2004**, *34*, 4049; (c) Tsoukala, A.; Bjørsvik, H.-R. *Org. Process Res. Dev.* **2011**, *15*, 673; (d) Duveau, D. Y.; Arce, P. M.; Schoenfeld, R. A.; Raghav, N.; Cortopassi, G. A.; Hecht, S. M. *Bioorg. Med. Chem.* **2010**, *18*, 6429; (e) Morimasa, A. *Jpn. Kokai Tokkyo Koho* **1996**, JP 08239340; (f) Ma, W.; Li, D.-W.; Sutherland, T.-C.; Li, Y.; Long, Y.-T.; Chen, H.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 12366; (g) Okamoto, K.; Watsumoto, M.; Watanabe, M.; Kawada, M.; Imamoto, T.; Imada, I. *Chem. Pharm. Bull.* **1985**, *33*, 3745.
6. (a) Zhao, W.; Chen, X.-L.; Yuan, J.; Qu, L.; Duan, L.; Zhao, Y.-F. *Chem. Commun.* **2014**, 2018; (b) Liu, B.; Gu, L.; Zhang, J. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 104; (c) Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F. *Chem. Lett.* **1992**, 1299; (d) Asin-Cayuela, J.; Manas, A. R.; James, A. M.; Smith, R. A.; Murphy, M. P. *FEBS Lett.* **2004**, *571*, 9; (e) Angerer, H.; Nasiri, H. R.; Niedergesäß, V.; Kerscher, S.; Schwalbe, H.; Brandt, U. *Biochim. Biophys. Acta* **2012**, *1817*, 1776; (f) Pei, Z.; Gustavsson, T.; Roth, R.; Frejd, T.; Hägerhäll, C. *Bioorg. Med. Chem.* **2010**, *18*, 3457; (g) Ma, W.; Zhou, H.; Ying, Y.; Li, D.; Chen, G.; Long, Y.; Chen, H. *Tetrahedron* **2011**, *67*, 5990; (h) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292.
7. (a) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3575; (b) Matthew, A. *Med. Chem. Commun.* **2011**, *2*, 1135; (c) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.
8. (a) Wang, J.; Yang, J.; Yang, B.; Sun, J.; Yang, T. *J. Chem. Res.* **2010**, *34*, 717; (b) Wang, J.; Yang, J.; Yang, B.; Hu, X.; Sun, J.; Yang, T. *J. Chem. Res.* **2010**, *34*, 724; (c) Wang, J.; Yang, J.; Zhou, R.-G.; Yang, B.; Wu, Y.-S. *J. Chem. Res.* **2011**, *35*, 431; (d) Wang, J.; Yang, J.; Zhou, R.-G.; Yang, B.; Wu, Y.-S. *J. Chem. Res.* **2011**, *35*, 428; (e) Wang, J.; Zhou, R.-G.; Wu, T.; Yang, T.; Qin, Q.-X.; Li, L.; Yang, B.; Yang, J. *J. Chem. Res.* **2012**, *36*, 121; (f) Wang, J.; Hu, X.; Yang, J. *Synthesis* **2014**, *46*, 2371; (g) Wang, J.; Li, S.; Hu, X.; Yang, J. *Org. Prep. Proced. Int.* **2014**, *46*, 469; (h) Wang, J.; Li, S.; Yang, T.; Yang, J. *Eur. J. Med. Chem.* **2014**, *86*, 710.
9. Xu, P.; Guo, S.; Wang, L.; Tang, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 5955.