J|A|C|S
COMMUNICATIONS

Published on Web 03/03/2006

Dual-Function Cinchona Alkaloid Catalysis: Catalytic Asymmetric Tandem Conjugate Addition−Protonation for the Direct Creation of Nonadjacent Stereocenters

Yi Wang, Xiaofeng Liu, and Li Deng*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110

Received January 16, 2006; E-mail: deng@brandeis.edu

The asymmetric construction of two nonadjacent stereocenters in an acyclic molecule is typically accomplished via a multistep process during which the two stereocenters are generated in separate steps.[1] A fundamentally more efficient strategy is to create both stereocenters from readily available achiral starting materials in one step via an asymmetric tandem reaction mediated by an external chiral reagent. Although notable progress has been made in the development of such asymmetric tandem reactions employing a stoichiometric amount of chiral reagents, the implementation of this powerful strategy with efficient catalytic control remains a formidable challenge.[2] In particular, we are interested in the development of catalytic asymmetric tandem conjugate addition−protonation employing trisubstituted carbon donors and α-substituted Michael acceptors, in view of the presence of 1,3-tertiary−quaternary stereocenters in numerous natural products and the lack of direct and versatile methods for the enantioselective constructions of such structural motifs.[3] To attain synthetically useful enantioselectivity and diastereoselectivity for such an asymmetric tandem reaction, the chiral catalyst is required to exercise efficient stereocontrol of both the C−C bond-forming nucleophilic addition and the following protonation. To our knowledge, this challenge has not yet been met with success.[4] In this Communication, we report the first realization of an efficient catalytic asymmetric tandem conjugate addition−protonation for the generation of 1,3-stereocenters and its application in the development of a conceptually new and concise asymmetric synthesis of the bromopyrrole alkaloid (−)-manzacidin A.

We recently developed the readily accessible and tunable 6′-OH cinchona alkaloids **1** (Figure 1) as highly efficient catalysts for enantioselective conjugate additions of various carbon donors to nitroalkenes, α,β-unsaturated sulfones, and enones.[5] On the basis of the transition-state model (**T1**) derived from our mechanistic studies,[5c,d] we envisaged that **1**, in addition to facilitating the enantioselective C−C bond-forming nucleophilic addition of a trisubstituted carbon donor to an α-substituted Michael acceptor, might also be able to effect the subsequent protonation of the transient enol intermediate in a stereoselective manner, as shown in Scheme 1. Consequently, 6′-OH cinchona alkaloids **1** could, in principle, serve as a dual-function chiral catalyst for the asymmetric tandem conjugate addition−protonation reaction to create the tertiary and quaternary stereocenters in an enantioselective and diastereoselective manner.

Following these considerations, we began to investigate 6′-OH cinchona alkaloids **1** as catalysts for the asymmetric tandem conjugate addition−protonation with trisubstituted carbon donors and 2-chloroacrylonitrile (**2**). This asymmetric tandem reaction is particularly attractive to us as the synthetic versatility of the chloride, in combination with a substantial scope of the trisubstituted carbon donors, could allow this reaction to provide a highly versatile catalytic approach for the asymmetric creation of 1,3-tertiary−quaternary stereocenters. Catalyst screening studies with α-cyanoketone **3a** and **2** were performed in toluene at room temperature (Table 1). The reaction catalyzed by QD-**1a** afforded the best enantioselectivity as well as diastereoselectivity and, at 10 mol % catalyst loading, afforded the desired product **4a** in 75% ee and 3.1:1 dr (Table 1, entry 8). When the reaction was carried out with 20 mol % of QD-**1a** and the reaction concentration was decreased from 1.0 to 0.1 M, the ee and dr were improved to 91% and 7:1, respectively (entry 10). In addition to its synthetic significance, the dramatically higher diastereoselectivity afforded by QD-**1a** than that afforded by DABCO and other cinchona alkaloids also has important mechanistic implications, as it excludes the possibility that the stereoselective protonation is due to substrate control by the quaternary stereocenter formed in the nuclephilic addition instead of due to catalyst control by QD-**1a**.

Following these promising results, we examined the scope of the **1a**-catalyzed tandem conjugate addition−protonation. As summarized in Table 2, the catalyst tolerates alterations of the cyclic donor in terms of ring size as well as the electronic and steric properties of the substituents attached to the nucleophilic carbon. Thus, reactions of various cyclic α-cyanoketones **3a**−**d** and β-ketoesters **3e**−**h** with **2** proceeded in 71−95% yield to afford the corresponding adducts **4a**−**h** containing the 1,3-tertiary−quaternary stereocenters in 7−25:1 dr, and the major diastereomers were produced in 91−99% ee.

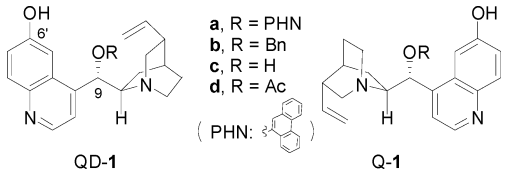
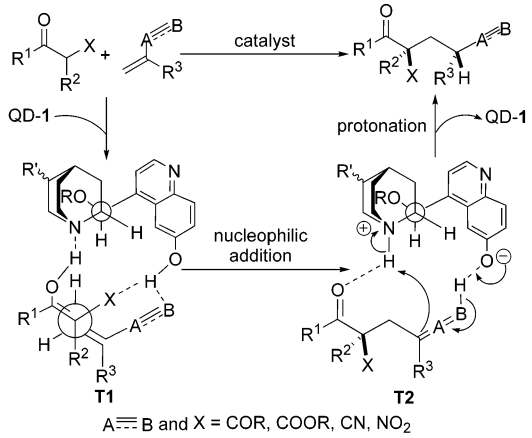


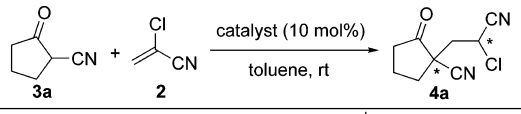
Figure 1. C6′-OH cinchona alkaloid derivatives.

Scheme 1. Proposed Model for the Modified Cinchona Alkaloid-Catalyzed Conjugate Additions



10.1021/ja060312n CCC: $33.50

Table 1. Optimization of Reaction Conditions Using Model Substrates[a]

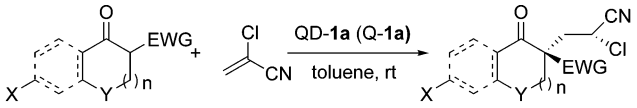


3a **2** **4a**

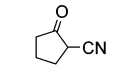
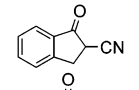
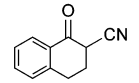
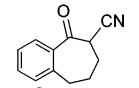
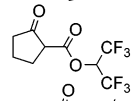
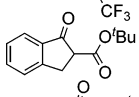
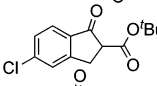
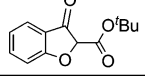
entry	catalyst	toluene (mL)	time (hr)	conv.[b] (%)	d.r.[b]	ee[c] of major isomer (%)
1	DABCO	0.05	20	85	1.2:1	0
2	$(DHQD)_2PHAL$	0.05	20	82	0.9:1	13
3	$(DHQD)_2AQN$	0.05	20	36	0.8:1	23
4	$(DHQD)_2PYR$	0.05	20	95	0.8:1	33
5	DHQD-PHN	0.05	20	74	1.2:1	13
6	QD-**1c**	0.05	20	90	1.6:1	16
7	QD-**1b**	0.05	20	95	2.3:1	57
8	QD-**1a**	0.05	20	93	3.1:1	75
9	QD-**1a**	0.50	60	71	5.0:1	90
10	QD-**1a**[d]	0.50	60	99	7.0:1	91

[a] Unless noted, reactions were carried out with 0.05 mmol of **3a**, 0.2 mmol of **2** in toluene with 10 mol % of catalysts at room temperature, see Supporting Information for the structure of catalysts. [b] Determined by ^{1}H NMR analysis. [c] Determined by GC analysis. [d] Reaction was run with 20 mol % of catalyst.

Table 2. Conjugate Addition-Protonation with Cyclic Michael Donors Catalyzed by QD-**1a** and Q-**1a** (in parentheses)[a]



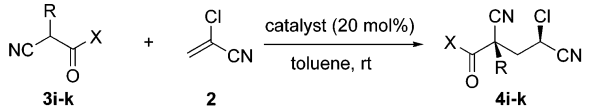
3a-h **2** **4a-h**

entry	Michael donor		catalyst loading (mol%)	time (hr)	yield[b] (%)	d.r.[c]	ee[d] of major isomer (%)
1		**3a**	20	60(96)	93(89)	7:1(5:1)	91(85)
2		**3b**	10	4(7)	95(95)	20:1(20:1)	96[f](93)
3		**3c**	20	72(96[e])	87(92)	11:1(8:1)	91(87)
4		**3d**	10	24(72)	88(92)	25:1(25:1)	95(94)
5		**3e**	20	48(48)	71(74)	9:1(8:1)	94(93)
6		**3f**	10	24(48)	94(91)	17:1(17:1)	98(98)
7		**3g**	10	24(24)	81(82)	20:1(13:1)	99[f](98)
8		**3h**	20	48[g](48[g])	75(78)	20:1(17:1)	98(97)

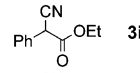
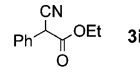
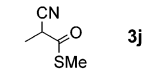
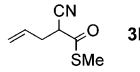
[a] Unless noted, reactions were carried out with 0.1 mmol of **3**, 0.4 mmol of **2** in 1.0 mL of toluene with QD-**1a** at room temperature. The results in parentheses were obtained with Q-**1a** to give opposite enantiomer. See Supporting Information for details. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC or GC analysis. [e] 0.8 mmol of **2** was used instead. [f] Absolute configuration were determined by X-ray analysis. See Supporting Information for details. [g] 0.25 mL of toluene was used.

However, catalyst QD-**1a** was found to be ineffective for acyclic trisubstituted carbon donors. The reaction of α-phenyl α-cyanoacetate **3i** to **2** catalyzed by QD-**1a** occurred in low dr (2:1) and moderate enantioselectivity (Table 3, entry 1). Importantly, our

Table 3. Asymmetric Conjugate Addition−Protonation with Acyclic Michael Donors[a]



3i-k **2** **4i-k**

entry	Michael donor		catalyst	time (hr)	yield[b] (%)	d.r.[c]	ee[d] of major isomer (%)
1		**3i**	QD-**1a**	96	99[f]	2:1	79
2		**3i**	QD-**1d**	96[e]	85	4:1	88
3		**3j**	QD-**1d**	96	71	10:1	93[g]
4		**3k**	QD-**1d**	96	60[h]	7:1	89

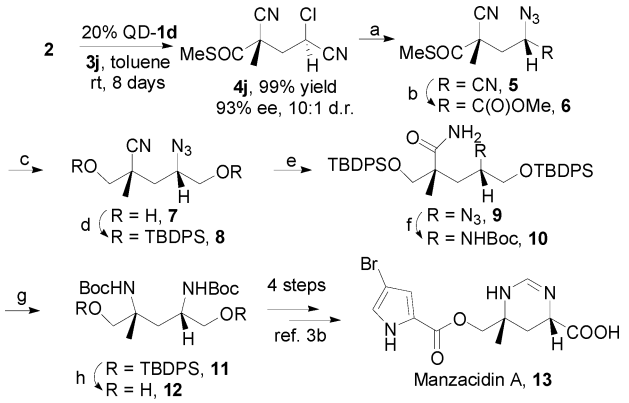
[a] Unless noted, reactions were carried out with 0.1 mmol of **3**, 0.8 mmol of **2** in 1.0 mL of toluene with 20 mol % catalyst at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. [d] Determined by HPLC or GC analysis; see Supporting Information for details. [e] 0.5 mL of toluene was used. [f] Conversion instead of yield was listed. [g] Absolute configuration was confirmed through the stereoselective formal total synthesis of (−)-manzacidin A as described below. [h] Pure diastereomer was obtained.

model studies with **3a** and **2** revealed that the readily tunable C9 substituent of catalysts **1** had a significant impact on both the enantioselectivity and diastereoselectivity for the asymmetric tandem reaction (Table 1, entries 6−8). This prompted us to improve the efficiency of catalysts **1** for the tandem asymmetric conjugate addition−protonation with acyclic donors by modifications of the C9 substituent. Subsequently, we found that a 6′-OH cinchona alkaloid bearing a C9-carboxylate substituent[6] (QD-**1d**) afforded significantly improved enantioselectivity and diastereoselectivity over those afforded by QD-**1a** (Table 3, entry 2 vs 1). Significantly, reactions of a range of acyclic donors with **2** in the presence of QD-**1d** occurred in 4−10:1 dr and generated the major diastereomer in 88−93% ee (Table 3, entries 2−4).

In light of the unique capacity of this asymmetric tandem reaction in generating stereocomplexity, we began to develop new and concise asymmetric total synthesis of biologically interesting natural products containing 1,3-tertiary−quaternary centers. Due to the limited supply of manzacidin A (**13**) from natural sources, this bromopyrrole alkaloid became an attractive target for our total synthesis studies.[7] While two highly stereoselective syntheses of the closely related manzacidin C in 10 steps were reported by Du Bois[3a] and Lanter and co-workers,[3c] respectively, the development of a concise route to manzacidin A with satisfactory stereocontrol proved to be more difficult.[8] Although Ohfune and co-workers reported the first highly stereoselective synthesis of manzacidin A (**13**), it was implemented with chiral anxiliary and substrate control in 22 steps.[3b] Thus, the development of a highly stereoselective route that is not only short in reaching **13** but also suitable for the preparations of analogues of **13** remains a desirable yet challenging goal.

We envisaged that the tetrahydropyrimidine core bearing the 1,3-tertiary−quaternary stereocenters could be constructed via stereospecific transformations of intermediate **4j**, which is accessible directly in excellent yield via the highly diastereoselective and enantioselective tandem conjugate addition−protonation catalyzed by QD-**1d** (Table 3, entry 3).[9] Substitution of the chloride with azide, followed by selective alcoholysis of the sterically less

Scheme 2. Asymmetric Formal Synthesis of (−)-Manzacidin A[a]



[a] Reagents and conditions: (a) NaN_3, DMSO, rt, 56%, 10:1 dr. (b) TMSCl, MeOH, 0 °C, 95%, 10:1 dr. (c) $NaBH_4$, $Hg(OAc)_2$, EtOH, 0 °C, 83%, 9:1 dr. (d) TBDPSCl, imidazole, DMF, rt, 91%, 10:1, dr. (e) $[PtH(PMe_2OH)(PMe_2O)_2H]$, EtOH, H_2O, 80 °C, 97%, 93% ee, 10:1 dr. (f) Pd/C, Boc_2O, EtOH, H_2, rt, 68%, 91% ee, nd, dr. (g) $Pb(OAc)_4$, ^{t}BuOH, reflux, 83%, 11:1 dr. (h) TBAF, THF, rt, 70%, 92% ee, single diastereomer. TBDPS = *tert*-butylchlorodiphenylsilane.

hindered nitrile group, converted **4j** to **6** without compromising the stereochemical integrity of the tertiary stereocenter.[10] Both the thioester and ester groups in **6** were then reduced with sodium borohydride.[11] Following protection of the resulting diol, the hydration of the sterically highly hindered nitrile group in **8** was performed by Parkins' procedure to provide amide **9** in excellent yield.[12] A one-pot transformation of the azide in **9** into the corresponding Boc-protected amine furnished amide **10**,[13] which readily underwent Hofmann rearrangement under the conditions reported by Burgess to directly form **11** in 83% yield.[14] After the removal of the TBDPS group, diol **12** was isolated in 70% yield as a pure diastereomer in 92% ee. As diol **12** was previously converted to manzacidin A (**13**) in four steps by Ohfune,[3b] this nine-step synthesis of **12** from **2** constitutes a formal asymmetric total synthesis of manzacidin A (**13**) in 13 steps (Scheme 2). Importantly, the ability of catalyst QD-**1d** to tolerate the structural change of the α-substituent of the α-cyanothioester should enable preparations of analogues of manzacidin A (**13**) by this route.

In summary, we have developed an unprecedented catalytic tandem asymmetric conjugate addition−protonation reaction with C6′-cinchona alkaloids **1** as dual-function chiral catalysts. This reaction establishes a new and versatile catalytic approach for the one-step construction of 1,3-tertiary−quaternary stereocenters. The synthetic value of this approach in the context of total synthesis of natural products is illustrated in the development of a concise and highly stereoselective route to (−)-manzacidin A. Mechanistic studies are underway to verify our hypothesis (Scheme 1) of a network of hydrogen bonds between the reacting substrates and C6′-OH cinchona alkaloids **1** as the factor responsible for the stereoselective generation of both stereocenters through this tandem asymmetric reaction. Notably, the absolute stereoconfigurations of products **4b**, **4g**, and **4j**, derived respectively from the corresponding cyclic donors (**3b**, **3g**) and acyclic donor (**3j**), are consistent with our mechanistic proposals. Future studies in our laboratories will also be directed to define the scope and expand the synthetic utility of this reaction.

Acknowledgment. We thank Mr. Jason Unger for his assistance with the preparation of catalyst QD-**1d**. We are also grateful for the generous financial support from National Institutes of Health (GM-61591).

Note Added after ASAP Publication. After this paper was published ASAP on March 3, 2006, names were corrected in refs 1d, 4e, and 14. The corrected version was published ASAP on March 14, 2006.

Supporting Information Available: Experimental procedures and characterization of the products; X-ray analysis data (CIF) for **4b**,**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected recent examples, see: (a) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724−14725. (b) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3258−3260. (c) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911−2914. (d) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178−16179. (e) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846−6847. (f) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019. (g) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518−6519. (h) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640−5641. (i) Myers, A. G.; Yang, B. H.; Chen, H.; Mckinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(2) For asymmetric synthesis of 1,5-chiral diols, see: (a) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644−13645. For construction of 1,3-tertiary−quaternary stereocenters with chiral anxiliary-directed tandem conjugate addition−protonation, see: (b) Keller, L.; Camara, C.; Pinheiro, A.; Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **2001**, *42*, 381−383. For diastereoselective methods, see: (c) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48−49. (d) Wang, X.; Meng, Q.; Perl, N. R.; Xu, Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12806−12807. (e) Wang, X.; Meng, Q.; Nation, A. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672−10673.

(3) For asymmetric total syntheses of manzacidins, see: (a) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950−12951. (b) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708−10709. (c) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905−5907. For asymmetric syntheses of (−)-dysiherbaine, see: (d) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216−5217. (e) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638. For the asymmetric synthesis of (−)-nakadomarin A, see: Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2020−2023.

(4) For a review of catalytic tandem asymmetric reactions triggered by conjugate addition, see: (a) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354−366. For selected recent examples that create adjacent stereocenters, see: (b) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710−15711. (c) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051−15053. (d) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036−15037. (e) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306−5310. (f) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874−3879. (g) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472−9473. For examples of catalytic asymmetric tandem conjugate addition−protonation for the creation of two adjacent stereocenters, see: (h) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390−2391. (i) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716−10717.

(5) (a) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947−950. (b) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948−8949. (c) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105−108. (d) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906−9907.

(6) See Supporting Information for the preparation of QD-**1d**.

(7) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574−4576.

(8) As described in ref 3a, Wehn and Du Bois also reported a 10-step asymmetric total synthesis of manzacidin A in which the tertiary amine is generated by a stereospecific intramolecular C−H bond amination of the corresponding methine. The required chiral methine precursor was produced via a catalytic asymmetric hydrogenation in moderate stereoselectivity.

(9) 99% isolated yield was obtained after a reaction time of 8 days.

(10) (a) Effenberger, F.; Kremser, A.; Stelzer, U. *Tetrahedron: Asymmetry* **1996**, *7*, 607−618. (b) Basu, M. K.; Luo, F.-T. *Tetrahedron Lett.* **1998**, *39*, 3005−3006.

(11) Yu, C.-M.; Lee, J. Y.; Chun, K.; Lee, J.; Lee, Y.-A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3622−3626.

(12) Ghaffar, T.; Parkins, A. *J. Mol. Catal. A: Chem.* **2000**, *160*, 249−261.

(13) Qin, D.; Zha, H.; Yao, Z. *J. Org. Chem.* **2002**, *67*, 1038−1040.

(14) Burgess, K.; Ke, C. *Synthesis* **1996**, 1463−1467.

JA060312N