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Highly Efficient Formal Synthesis of Cephalotaxine, Using the Stevens Rearrangement−Acid Lactonization Sequence as A Key Transformation

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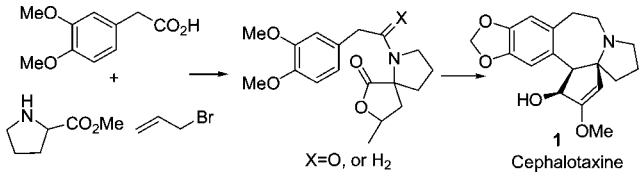

Cephalotaxine (**1**), the major alkaloid isolated from *Cephalotaxus species*, has attracted considerable attention due to the promising antitumor activity of several of its derivatives and its unique structural features. Herein we describe a highly efficient formal synthesis of **1** employing the [2,3]-Stevens rearrangement−acid lactonization sequence as a key transformation from readily available (3,4-dimethoxyphenyl)acetic acid, methyl prolinate, and allyl bromide.

Cephalotaxine (**1**, CET), the parent member of the *Cephalotaxus* alkaloids,[1] has a unique ring skeleton containing an unusual 1-azaspiro[4,4]nonane moiety fused to a benzazepine moiety. The structural characteristics of CET and the clinically proven yet intriguing antitumor therapeutic potentials of its naturally occurring ester derivatives (harringtonine and homoharringtonine) have attracted a long-standing interest in their chemical synthesis.[2] Herein we describe a highly efficient synthesis of CET (**1**) employing the [2,3]-Stevens rearrangement−acid lactonization sequence as a key transformation.

Our retrosynthesis of **1** led to the tetracyclic core **2** and spiroenone **3** (Figure 1). The transformation of **2b** → **1** and **3** → **2**[3] has been demonstrated by Hanaoka et al.[4] and Li et al.,[5] respectively. We assumed that **3** should be available by a combination of lactone reduction, swern oxidation, and intramolecular keto-aldehyde aldol condensation starting from the

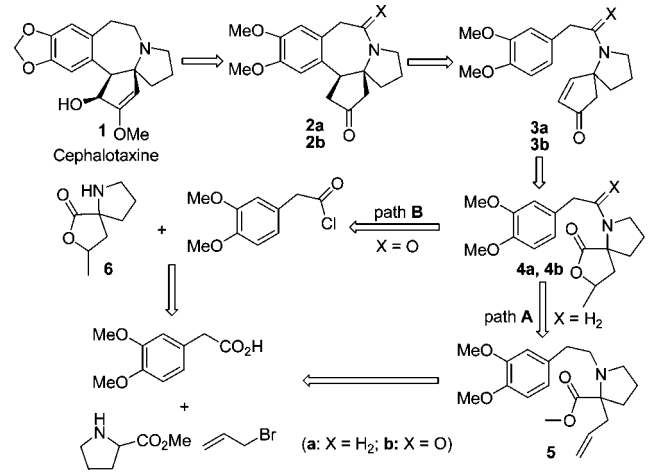

FIGURE 1. Retrosynthesis analysis of cephalotaxine.

spirolactone **4**. The precursor **4** could be derived either from the acid-lactonization of γ-en-carboxylate **5** (path **A**, X = H_2) or from the condensation of 3,4-dimethoxyphenacetyl chloride with spirolactone **6** (path **B**, X = O). In path **A** and path **B**, (3,4-dimethoxyphenyl) acetic acid, methyl prolinate, and allyl bromide were the starting materials. These materials are commercially available.

As shown in Scheme 1, the synthesis of **3a** commenced from 3,4-dimethoxyphenyl acetic acid **7**, which was converted to iodide **8** with 82% overall yield.[6] Reaction of iodide **8** with methyl prolinate in CH_3CN at room temperature for 8 h yielded the nitrogen alkylation product **9** in 87% yield. Workup of **9** with allyl bromide in the presence of K_2CO_3 in CH_3CN furnished the γ-en-carboxylate **5** via a facile [2,3]-Stevens rearrangement of the resulting allyl quaternary ammonium salt **10** in 85% yield. The Stevens rearrangement that we modified (K_2CO_3 in CH_3CN) was superior to the technique reported in the literature (KOBu^t-DMSO-THF).[7] Thus, the quaternary carbon center α to the nitrogen of the pyrrolidine, which was key in the total synthesis of cephalotaxine, was successfully produced[8] in one pot at the outset of our synthesis. With **5** in hand, we turned our attention to the synthesis of spiroenone **3a**. **3a**, or its derivatives, can be prepared by using a Wacker oxidation as the key transformation. However, a stoichiometric amount of $PdCl_2$ is required. Using this method, our observed

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(2) For a recent total synthesis, see: Hameed, A.; Blake, A. J.; Hayes, C. J. *J. Org. Chem.* **2008**, *78*, 8045, and references cited therein.

(3) For possible transformation from **3** to **1** via an alternative pathway, see relevant total synthesis of cephalotaxine: (a) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439. (b) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (c) Sha, C. K.; Young, J. J.; Yeh, C. P.; Chang, S. C.; Wang, S. L. *J. Org. Chem.* **1991**, *56*, 2694. (d) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (e) Tieze, L. F.; Shirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264. (f) Ikeda, M.; Hirose, K.; El, Bialy, S. A. A.; Sato, T.; Yakura, T.; Bayoma, S. M. M. *Chem. Pharm. Bull.* **1998**, *46*, 1084. (g) Suga, S.; Watanabe, M.; Yoshida, J. I. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (h) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.

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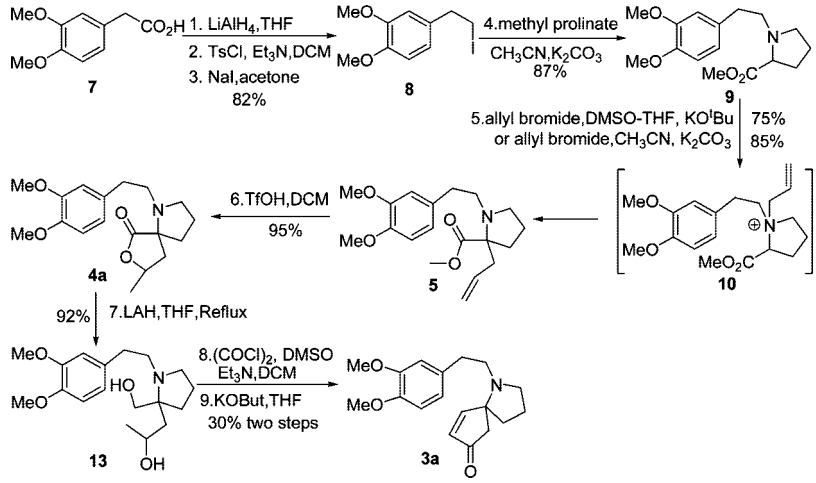
SCHEME 1. Preparation of Enone 3a



yield was low.[9] Thus, we attempted to obtain spiroenone **3a** via acid-lactonization of **5**. To our surprise, although iodolactonization of γ-en-carboxylic acid was widely applied in the total synthesis of natural products, the acid-lactonization of γ-en-carboxylate has seldom been reported.[10] Among various acidic systems (HCl, H_2SO_4, PPA, MsOH, TFA, TsOH), triflic acid (5 equiv, DCM, rt, 5−7 min) gave the highest yield (95%). It also requires the simplest experimental scheme for transforming **5** to amino spirolactone **4a**. The direct iodolactonization of **5** led to a slow decomposition of the substrate. This is presumably due to the existence of nitrogen atom. The unstable keto-aldehyde intermediate is produced by subjecting **4a** to $LiAlH_4$ reduction[11] and subsequent Swern oxidation[12] of the resulting diol **13**. An attempt to oxidize diol **13** with PCC and PDC failed because the α-amino aldehyde was sensitive to decomposition under an acid environment. For this reason, the crude product was condensed, without purification by column chromatography with KO^{t}Bu-THF, to afford spirocyclopentenone **3a**.[13]

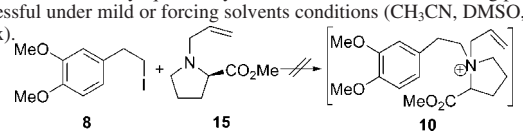
Thus we have accomplished a formal synthesis of CET, using a facile [2,3- Stevens rearrangement and acid-lactonization as the key transformation steps. The instability of the keto-aldehyde intermediate was responsible for the low overall yields (30%) of Swern oxidation and Aldol condensation. So we developed a modified synthesis route (path **B**), which employed amido spirocyclopentenone **3b** as a precursor for CET synthesis.

Following a procedure analogous to the one mentioned above, we first synthesized the spirolactone **6** from readily available methyl prolinate **14** by the following sequence (Scheme 2): (1) N-allylation of methyl prolinate **14** (allyl bromide, K_2CO_3, DMF), (2) [2,3]-Stevens rearrangement of the resulting quaternary ammonium by the reaction of **15** with benzyl bromide in CH_3CN, and (3) acid-lactonization of **16** (5 equiv of TfOH, DCM, rt) followed by debenzylation through catalytic hydrogenation (Pd/C, H_2).[14] Condensation of spirolactone **6** with 3,4-dimethoxyphenacetyl chloride produced the amide spirolactone **4b**, which was subjected to selective reduction with $LiBH_4$ to give diol **18**.[15] To our delight, Swern oxidation of diol **18** produced the stabilized amido keto-aldehyde **19** in almost quantitative yield. The treatment of **19** with K_2CO_3, under MeOH-H_2O[16] conditions, produced the amido spirocyclopentenone **3b**. According to Li et al.'s procedure,[5] triflic acid mediated Friedel−Crafts cyclization of amido spirocyclopentenone **3b** furnished **2b**, whose spectra (^{1}H NMR, ^{13}C NMR, IR) were in full accord with those reported by Hanaoka et al.[4] The modified sequence outlined in Scheme 2 constitutes a highly efficient formal synthesis of CET. The overall yield from methyl prolinate **14** to **3b**, through eight-stage operations, is ca. 51%.

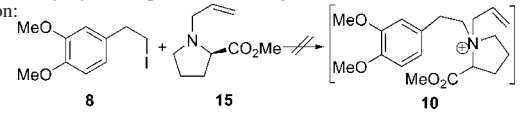
In summary, sequential application of the [2,3]-Stevens rearrangement and acid-lactonization reaction provides a rapid entry to the synthetically challenging tetracyclic core **2b** (**2a**) of cephalotaxine. This process should have general application in bioactive alkaloid synthesis. The efficiency and practicality of the synthesis follows from its brevity. The availability of starting materials, the operationally simple reaction with inexpensive reagents, and high overall yield make it especially suitable for large-scale production. The 10−50 g scale of **2b** was easily available in our laboratory.

Currently, we are exploring various conditions to transform **2b** to cephalotaxine via simpler methods than those used by

(8) Preparation of the allyl quaternary ammonium **10**, via the following path, was unsuccessful under mild or forcing solvents conditions (CH_3CN, DMSO, rt → reflux).



(9) The unsuccessful transformation of **5** → **12**, **11** → **13** was probably attributed to the stronger coordination of the nitrogen atom to $PdCl_2$ and $CuCl_2$. Viscous brown jelly was produced during the course of the following reaction:



(10) For reported acid-lactonization reaction of γ-en-carboxylate, see: (a) Amonkar, C. P.; Tilve, S. G.; Parameswaran, P. S. *Synthesis* **2005**, *14*, 2341. (b) Guo, M.; Varady, L. *Tetrahedron Lett.* **2002**, *43*, 3677. (c) Ila Hiriyakkanavar, A.-D.; Junjappa, H. *Tetrahedron* **1987**, *43*, 5367. (d) Tiecco, M.; Tingoli, M.; Testaferri, L.; Bartoli, D. *Synth. Commun.* **1989**, *19*, 2817.

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(13) Considerable difficulty was encountered in finding conditions suitable for the base-catalyzed aldol condensation of keto-aldehyde intermediate. Among the conditions (K_2CO_3/MeOH, KOH/MeOH, proline/EtOH, proline/DMSO) examined, the only effective one was the KO^{t}Bu/THF system, which furnished the amino spirocyclopentenone **3a**. For information on this system, see: Freiria, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, *60*, 2673.

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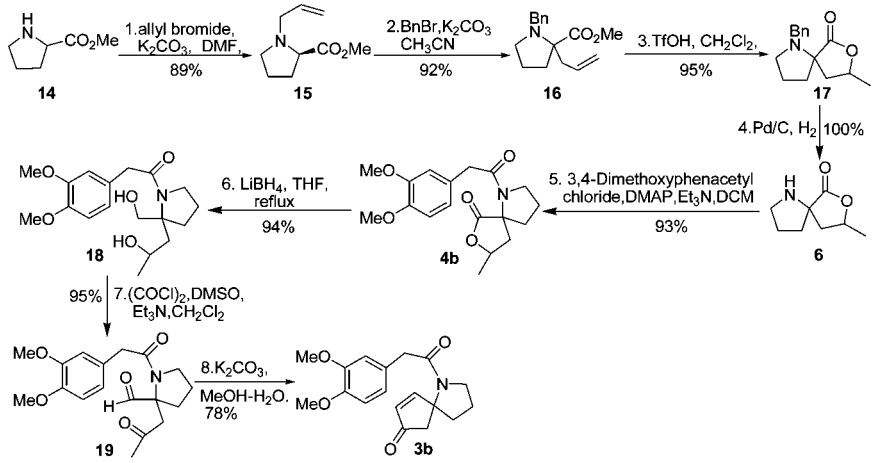
SCHEME 2. Modified Highly Efficient Synthesis of 3b



Hanaoka.[3] An application of this method to the synthesis of optically active cephalotaxine and its analogues is now in progress.

Experimental Section

4-(2-Iodoethyl)-1,2-dimethoxybenzene (8). To a solution of $LiAlH_4$ (0.39 g, 10 mmol) suspended in dry THF (20 mL) was added 3,4-dimethoxyphenyl acetic acid **7** (0.98 g, 5 mmol) at room temperature. The mixture was stirred for 30 min and then H_2O (0.39 mL), 15% aqueous NaOH (0.39 mL), and H_2O (1.17 mL) were added successively. After the mixture was stirring for 5 min, the produced aggregates were filtered out and the solvent was removed in vacuo to give the alcohol (0.86 g, 93%) as a colorless oil. To a cooled (0 °C) solution of alcohol (0.86 g, 4.73 mmol) in dry CH_2Cl_2 (8.0 mL) were added Et_3N (0.81 mL, 5.68 mmol) and tosyl chloride (1.10 g, 5.68 mmol). After the reaction mixture was stirred at room temperature for 30 min, CH_2Cl_2 (30 mL) was added and the mixture was washed with a saturated aqueous solution of Na_2CO_3 and brine successively. The organic phase was dried, concentrated, and subjected to column chromatography to give tosylate (1.51 g, 95%) as a colorless oil. A mixture of tosylate (1.50 g, 4.50 mmol) and sodium iodide (6.73 g, 44 mmol) in acetone (5.0 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and the solvent was evaporated. The residue was taken up in water (10 mL) and extracted with ethyl acetate and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of crude product eluting with petroleum ether−EtOAc (10/1) gave **8** as a colorless oil (1.20 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (t, J = 15.5 Hz, 2H), 3.28 (t, J = 15.5 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.67−6.70 (m, 2H), 6.76 (d, J = 8.0 Hz, 1H).

Methyl 1-(3,4-Dimethoxyphenethyl)pyrrolidine-2-carboxylate (9). A mixture of methyl prolinate (1.29 g, 10 mmol), compound **8** (2.92 g, 10 mmol), and K_2CO_3 (2.76 g, 20 mmol) in CH_3CN (15 mL) was brought to reflux for 5 h. The resulting mixture was cooled and diluted with EtOAc (150 mL). The organic layer was washed with water (3 × 10 mL) and brine (2 × 10 mL), then dried over anhydrous $MgSO_4$. After evaporation of the solvent in vacuo, the crude residue was purified by silica gel column chromatography eluting with petroleum ether−EtOAc (4/1) to give **9** as a colorless oil (2.55 g, 87%). IR (KBr) ν_{max} 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78−1.99 (m, 3H), 2.04−2.19 (m, 1H), 2.55−2.65 (m, 1H), 2.67−2.88 (m, 2H), 2.84−2.87 (m, 1H), 3.18−3.23 (m, 2H), 3.67 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 148.7, 147.2, 132.3, 120.3, 111.8, 111.1, 77.0, 65.9, 56.9, 55.7, 53.5, 51.8, 34.8, 29.3, 23.1; HRMS (ESI) *m/z* obsd. 294.1700 ([M + H]$^+$, calcd 294.1705 for $C_{16}H_{24}NO_4$).

Methyl 1-(3,4-Dimethoxyphenethyl)-2-allylpyrrolidine-2-carboxylate (5). A mixture of compound **9** (2.00 g, 6.8 mmol), allyl bromide (0.90 g, 8.8mmol), and dry K_2CO_3 (1.60 g, 12 mmol) in dry CH_3CN (20.0 mL) was stirred for 6 h at room temperature. The solvent was evaporated in vacuo and then water (20 mL) and ethyl acetate (100 mL) were added. The aqueous phase was extracted with ethyl acetate (30.0 mL), combined with the organic phase, and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo followed by column chromatography (petroleum ether−EtOAc, 5/1) gave **5** as a colorless oil (1.97 g, 85%). IR (KBr) ν_{max} 3071, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70−1.89 (m, 3H), 2.04−2.10 (m, 1H), 2.20−2.38 (m, 1H), 2.47−2.75 (m, 5H), 2.87−2.94 (m, 1H), 3.17−3.26 (m, 1H), 3.64 (s, 3H), 3.86 (s, 6H), 5.00−5.07 (m, 2H), 5.65−5.75 (m, 1H), 6.70−6.73 (m, 2H), 6.77−6.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 148.7, 147.3, 134.3, 133.1, 120.6, 117.7, 112.1, 111.2, 77.4, 77.9, 70.5, 55.9, 51.4, 39.1, 35.7, 33.8, 29.7, 21.7; HRMS (ESI) *m/z* obsd 334.2011 ([M + H]$^+$, calcd 334.2018 for $C_{19}H_{28}NO_4$).

Spirolactone (4a). To a solution of compound **5** (2.41 g, 7.3 mmol) in dry CH_2Cl_2 (10.0 mL) was added triflic acid (5.50 g, 36.5 mmol). After the solution was stirred for 7 min at room temperature, CH_2Cl_2 (100 mL) was added and the resulting mixture was washed with a saturated aqueous solution of Na_2CO_3 and brine. The organic phase was separated, dried, and concentrated. The crude residue was purified by flash column chromatogramphy on silica gel (petroleum ether−EtOAc 4/1) to give **4a** as a colorless oil (2.20 g, 95%). IR (KBr) ν_{max} 1763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J = 6.1 Hz, 3H), 1.87−2.08 (m, 5H), 2.17−2.22 (m, 1H), 2.69−2.89 (m, 4H), 3.06−3.87 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.40−4.50 (m,1H), 6.7−6.8 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 148.8, 147.4, 132.8, 120.6, 112.1, 111.2, 77.1, 73.4, 70.5, 55.9, 51.3, 39.8, 36.1, 35.6, 22.6, 21.8, 21.1; HRMS (ESI) *m/z* obsd 320.1867 ([M + H]$^+$, calcd 320.1862 for $C_{18}H_{26}NO_4$).

Diol (13). To a solution of $LiAlH_4$ (0.39 g, 10 mmol) suspended in dry THF (20.0 mL) was added spirolactone **4a** (2.22 g, 6.96 mmol) in dry THF (5.0 mL) under refluxing conditions. The resulting mixture was cooled to room temperature after refluxing for 30 min and then H_2O (0.39 mL), 15% aqueous NaOH (0.39 mL), and H_2O (1.17 mL) were added successively. After 5 min of stirring, the produced aggregates were filtered out and the solvent was evaporated in vacuum to give **13** as a colorless oil (2.04 g, 92%). IR (KBr) ν_{max} 3373 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.2 Hz, 3H), 1.46 (d, J = 16.2 Hz, 1H), 1.53−1.65 (m, 1H), 1.72−1.81 (m, 3H), 1.87−1.92 (m, 1H), 2.67−2.82 (m, 5H), 3.06−3.11 (m, 1H), 3.40 (d, J = 11.1 Hz, 1H), 3.55 (d, J = 11.1 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 3.84−3.92 (m, 1H), 6.72−6.74 (m, 2H), 6.78−6.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 147.4, 132.7, 120.1, 112.3, 77.3, 76.9, 66.7, 64.9, 55.9, 51.3, 50.4, 41.4, 35.6, 32.3, 25.7, 21.7; HRMS (ESI) *m/z* obsd 324.2170 ([M + H]$^+$, calcd 324.2175 for $C_{18}H_{30}NO_4$).

Amino Spirocyclopentenone (3a). To a cooled (−78 °C) solution of DMSO (3.74 g, 48 mmol) in dry CH_2Cl_2 (8.0 mL) was

added a solution of oxalyl chloride (2.86 g, 22.4 mmol) in dry CH_2Cl_2 (8.0 mL) over a period of 6 min then the mixture was stirred for 10 min. Next a solution of diol (3.38 g, 10 mmol) in dry CH_2Cl_2 (10.0 mL) was added to the mixture at −78 °C. After 15 min at the same temperature, Et_3N (5.06 g, 50.0 mmol) was added and the solution was allowed to warm to room temperature. The mixture was quenched by addition of water (10 mL) and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, then dried and concentrated. The residue without further purification was solved in dry THF (10 mL) and ^{t}KOBu (1.12 g, 10 mmol) was added. After 20 min of stirring at room temperature, the solvent was evaporated under vacuum. The residue was taken up in water (15.0 mL) and extracted with ethyl acetate (3 × 50.0 mL). The combined organic phase was dried, concentrated, and subjected to column chromatography (petroleum ether−EtOAc 1/1) to give **3a** as a colorless oil (0.91 g, 30%). IR (KBr) ν_{max} 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79−2.04 (m, 4H), 2.07 (d, J = 18.4 Hz, 1H), 2.42−2.52 (m, 3H), 2.61−2.79 (m, 3H), 3.10−3.26 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 6.12 (d, J = 5.6 Hz, 1H), 6.67−6.70 (m, 3H), 7.33 (d, J = 5.6 Hz, 1H); HRMS (ESI) m/z obsd 302.1757 ($[M + H]^+$, calcd 302.1756 for $C_{18}H_{24}NO_3$).

Acknowledgment. We thank the National Nature Science Foundation (20502023) for financial support.

Supporting Information Available: Experimental procedures and spectral data of compounds **15**−**17**, **6**, **18**, **19**, and **2b**−**4b**, and ^{1}H and ^{13}C NMR spectra for all compounds characterized in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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