

HETEROCYCLES, Vol. 69, 2006, pp. 497 - 504. © The Japan Institute of Heterocyclic Chemistry
Received, 1st July, 2006, Accepted, 27th July, 2006, Published online, 28th July, 2006. COM-06-S(O)37

SHORT STEP SYNTHESIS OF NATURAL 2-ARYLQUINOLONES BASED ON IRIIDIUM-CATALYZED THREE-COMPONENT COUPLING QUINOLINE SYNTHESIS

Takayuki Nakajima, Takashi Inada, and Isao Shimizu*

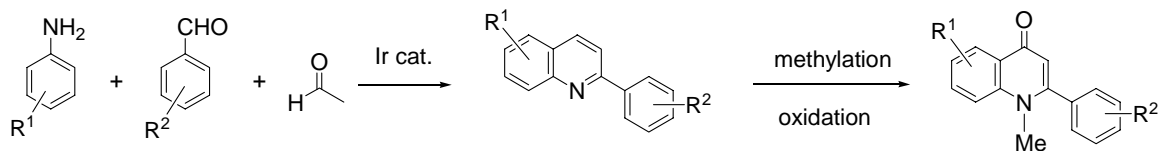
Department of Applied Chemistry, Graduate School of Science and Engineering,
Waseda University, Okubo 3-4-1, Shinjuku-ku, Tokyo 169-8555,
Japan. E-mail: shimizui@waseda.jp

Abstract – Eduline (**1a**), graveoline (**1b**), and 6-methoxy-2-(4-methoxyphenyl)-1-methylquinolone (**1c**) were synthesized by iridium-catalyzed three-component coupling reaction. Reaction of an aniline, an aromatic aldehyde, and acetaldehyde gave the corresponding substituted quinoline. Using 1,1-dimethoxyethane instead of acetaldehyde, the three component coupling reactions were also carried out to give the quinolines in higher yields. *N*-Methylation of the quinolines with methyl triflate followed by oxidation with potassium ferricyanate gave the quinolones.

INTRODUCTION

Naturally occurring 2-aryl-4(1*H*)-quinolinones (2-aryl-4-quinolones), eduline (**1a**)¹ and graveoline (**1b**),² are isolated from the family Rutaceae. These compounds and the related 2-arylquinolones have various biological activities, such as antimitotic and anti-tumor as well as antimicrobial activities.³ Representative synthetic methods of substituted quinolones, such as well-known Corand-Limpach reaction, involve stepwise reactions mainly based on condensation of aryl amine and β -keto esters followed by thermal cyclization.⁴ Their usefulness of the synthetic methods depends on availability of starting β -keto esters. Therefore more convenient methods starting with easily available materials have been expected.⁵ Recently J. Koyama reported a facile synthesis of 2-phenyl-4-quinolones involving converting methods of quinolines by the Diels-Alder reaction of enamines and 1,2,3-benzotriazines, however the preparation and treatment of 1,2,3-benzotriazines are not easy.^{6,7} the application using this method is limited due to poor availability of 1,2,3-benzotriazines. We have developed one-pot synthesis of 2-arylquinolines by an

iridium-catalyzed three component coupling reaction,⁸ which provides a facile synthesis of 2-aryl-4-quinolones as shown in the following Scheme 1.



Scheme 1. Facile synthesis of 2-aryl-4-quinolones.

RESULTS AND DISCUSSION

The results of iridium-catalyzed three-component coupling reaction for the synthesis of 2-arylquinolines are summarized in Table 1. The reaction of *p*-methoxyaniline (**2a**) ($R^1 = \text{OMe}$), benzaldehyde (**3a**), and acetaldehyde was carried out in the presence of a catalytic amount of the iridium complex, $[\text{IrCl}_2\text{H}(\text{cod})]_2$, in DMSO under oxygen atmospheres at 90 °C for 12 h to give 6-methoxy-2-phenylquinoline (**4a**) in 36% yield. Similarly, 2-arylquinolines (**4b**) and (**4c**) were obtained in 38 and 13% respectively by the reaction using the corresponding aromatic amines and aromatic aldehydes with acetaldehyde. Although the desired quinolines were obtained, the reaction also gives mixtures of other by-products due to using labile acetaldehyde. In order to improve the reaction, 1,1-dimethoxyethane instead of acetaldehyde was applied to the three-component coupling reaction and the 2-arylquinolones, (**4a**), (**4b**), and (**4c**), were obtained in 43, 41, and 35% respectively.

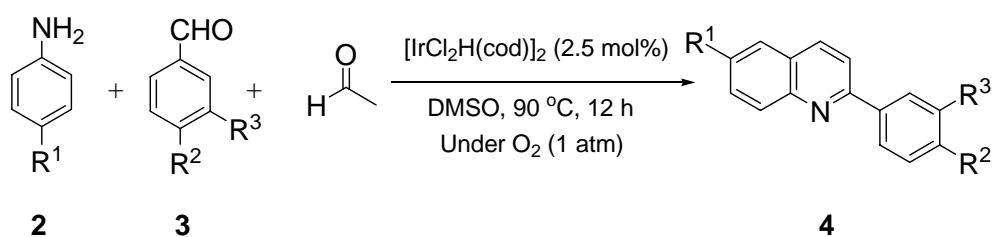
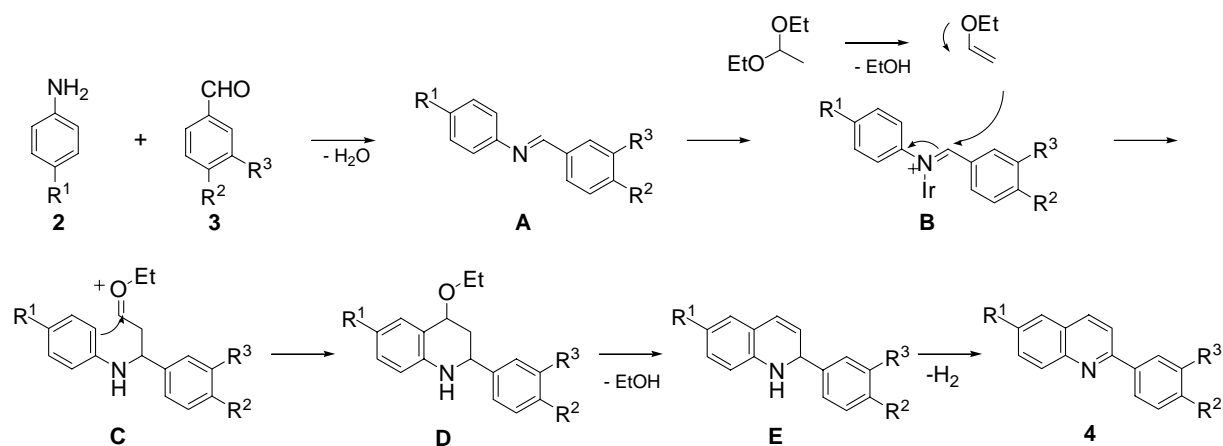


Table 1. Iridium-catalyzed synthesis of 2-arylquinolines (**4**) from arylamines (**2**) and arylaldehydes (**3**) and acetaldehyde

Product ^{a)}		
4a (36 %) (43 %) ^{b)}	4b (38 %) (41 %) ^{b)}	4c (13 %) (35 %) ^{b)}

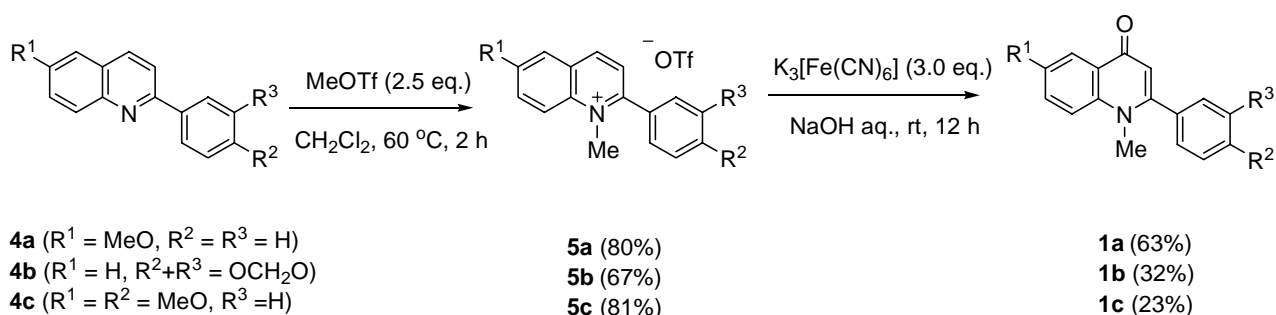
a) Isolated yield based on arylamine (**2**). b) 1,1-Dimethoxyethane was used, instead of acetaldehyde.

The reaction for the formation of **4** from **2**, **3**, and 1,1-dimethoxyethane can be explained as shown in Scheme 2. At first, the reaction of **2** and **3** gives the imine (**A**), which reacts with ethyl vinyl ether, obtained by elimination of ethanol from 1,1-dimethoxyethane, to afford the oxonium compound (**C**). Intramolecular Friedel-Crafts type reaction of **C** proceeds to form **D** and the subsequent elimination of ethanol followed by dehydrogenation of **E** to give the quinoline (**4**).



Scheme 2. Plausible mechanism for the formation of quinoline.

The one-step preparation of substituted quinolines, although further improvements seem to be still necessary, is useful for synthesis of biologically active quinolones. Next we examined oxidative conversion of quinolines to 4-quinolones.



Scheme 3. Synthesis of 2-arylquinolone from quinoline.

According to Koyama's procedure, methylation and oxidation were carried out. However the one-pot procedure without isolation of quinolinium salts did not give satisfactory results. Therefore the synthesis of **1** from **4** was carried out by a two-step procedure. Thus, methylation of **4** with methyl trifluoromethanesulfonate in CH_2Cl_2 at $60\text{ }^\circ\text{C}$ for 2 h gave the corresponding methyl adducts (**5**) in 80, 67,

and 81% yields respectively after recrystallization. Finally oxidation of the quinolinium salts (**5**) with potassium ferric cyanate in NaOH aq. at room temperature afforded eduline (**1a**), graveoline (**1b**), and 6-methoxy-2-(4-methoxyphenyl)quinoline (**1c**) in 63, 32, and 23% yields respectively.

In conclusion three step synthesis of 2-aryl-4-quinolones by iridium-catalyzed three component coupling reactions followed by methylation and oxidation was developed. This method provides useful methods for preparation of naturally occurring 2-arylquinolones and related compounds.

EXPERIMENTAL

¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ as a solvent using TMS as an internal standard on JEOL Lambda 500 spectrometers. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectroscopy (HRMS) and elemental analysis were performed by the Material Characterization Central Laboratory of Waseda University.

General procedure for the synthesis of 2-arylquinolines (4a – 4c). A mixture of arylamine (**2**) (1.0 mmol), arylaldehyde (**3**) (2.0 mmol), and [IrCl₂H(cod)]₂ (0.025 mmol) in DMSO (3 mL) was stirred at rt for 1 h under argon. Then acetaldehyde or 1,1-dimethoxyethane (1.5 mmol) was added into the resulting mixture, and the mixture was stirred at 90 °C for 12 h under oxygen (1 atm). The mixture was washed with PBS buffer solution (50 mL) and extracted with AcOEt (20 mL × 3). The organic layer was dried over MgSO₄. Removal of the solvent in vacuo, followed by chromatography on silica gel column (AcOEt / Hexane = 5 / 95), afforded **4**.

6-Methoxy-2-phenylquinoline (4a): pale yellow solid (from AcOEt / hexane, 85 mg, 36 %). mp 129-131 °C. ¹H NMR (500 MHz, CDCl₃) δ 3.93 (s, 3H, OCH₃), 7.08 (d, *J* = 2.7 Hz, 1H, aromatic H), 7.36 (dd, *J* = 9.2, 2.7 Hz, 1H, aromatic H), 7.41 – 7.44 (m, 1H, aromatic H), 7.48 – 7.51 (m, 2H, aromatic H), 7.82 (d, *J* = 8.6 Hz, 1H, aromatic H), 8.05 (d, *J* = 9.2 Hz, 1H, aromatic H), 8.09 – 8.12 (m, 3H, aromatic H); ¹³C NMR (125 MHz, CDCl₃) δ 55.5 (s, OCH₃), 105.0, 119.2, 122.3, 127.3, 128.1, 128.8, 128.9, 131.2, 135.5, 139.8, 144.4, 155.1, 157.7 (s, aromatic C); HRMS (FAB) calcd for C₁₆H₁₄NO [M + H]⁺ 236.1075, found 236.1086. Anal. Calcd for C₁₆H₁₃NO: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.30; H, 5.81; N, 5.77.

2-(Benzo[d][1,3]dioxol-5-yl)quinoline (4b): white solid (from AcOEt / hexane, 95 mg, 38 %). mp 91-93 °C (lit.,⁶ 95-96 °C). ¹H NMR (500 MHz, CDCl₃) δ 5.98 (s, 2H, CH₂), 6.89 (d, *J* = 8.2 Hz, 1H, aromatic H), 7.44 (dt, *J* = 7.5, 0.7 Hz, 1H, aromatic H), 7.59 (dd, *J* = 8.1, 1.6 Hz, 1H, aromatic H), 7.64 (dt, *J* = 7.5, 1.3 Hz, 1H, aromatic H), 7.67 (d, *J* = 1.6 Hz, 2H, aromatic H), 7.72 – 7.74 (m, 2H, aromatic H), 8.05 (d, *J* =

8.6 Hz, 1H, aromatic H), 8.11 (d, $J = 8.6$ Hz, 1H, aromatic H); ^{13}C NMR (125 MHz, CDCl_3) δ 101.4 (s, OCH_2), 105.2, 107.9, 108.5, 118.6, 121.7, 126.1, 127.4, 129.6, 129.7, 134.1, 136.7, 148.2, 148.4, 148.8 (s, aromatic C); HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{12}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 250.0868, found 250.0884.

6-Methoxy-2-(4-methoxyphenyl)quinoline (4c): colorless crystals (from AcOEt / hexane, 34 mg, 13 %). mp 128-131 °C. ^1H NMR (500 MHz, CDCl_3) δ 3.81 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.95 – 6.97 (m, 2H, aromatic H), 7.00 (d, $J = 2.9$ Hz, 1H, aromatic H), 7.29 (dd, $J = 9.3, 2.9$ Hz, 1H, aromatic H), 7.71 (d, $J = 8.6$ Hz, 1H, aromatic H), 7.96 (d, $J = 9.3$ Hz, 1H, aromatic H), 8.00 (d, $J = 8.8$ Hz, 1H, aromatic H), 8.02 – 8.03 (m, 2H, aromatic H); ^{13}C NMR (125 MHz, CDCl_3) δ 55.4, 55.5 (s, OCH_3), 105.1, 114.2, 118.8, 122.1, 127.8, 128.5, 131.0, 132.4, 135.4, 144.3, 154.7, 157.4, 160.5 (s, aromatic C); HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{16}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 266.1181, found 266.1163. Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.55; H, 6.03; N, 5.45.

General procedure for the synthesis of 5. To a stirred solution of 6-methoxy-2-phenylquinoline (**4**) (0.260 mmol) in CH_2Cl_2 (1.0 mL) was added MeOTf (0.071 mL, 0.650 mmol) and the resulting solution was stirred for 2 h at 60 °C. The reaction mixture was washed with brine and extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 . Removal of the solvent in vacuo afforded pale brown crystals. Recrystallization from CHCl_3 / AcOEt gave **5**.

6-Methoxy-*N*-methyl-2-phenylquinolinium trifluoromethanesulfonate (5a): colorless needles (83 mg, 80 %). mp 137-138 °C. ^1H NMR (500 MHz, CDCl_3) δ 3.97 (s, 3H, OCH_3), 4.46 (s, 3H, NCH_3), 7.53 (d, $J = 2.6$ Hz, 1H, aromatic H), 7.62 – 7.64 (m, 5H, aromatic H), 7.74 – 7.76 (m, 2H, aromatic H), 8.33 (d, $J = 9.7$ Hz, 1H, aromatic H), 8.87 (d, $J = 8.4$ Hz, 1H, aromatic H); ^{13}C NMR (125 MHz, CDCl_3) δ 42.6, 56.4, 107.9, 121.0, 124.9, 128.9, 129.3, 129.6, 130.9, 131.8, 132.7, 135.5, 144.8, 156.7, 160.0; HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{16}\text{NO}$ $[\text{M} - \text{OTf}]^+$ 250.1226, found 250.1226. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{NO}_4\text{S}$: C, 54.13; H, 4.04; N, 3.51. Found: C, 54.04; H, 4.23; N, 3.40.

2-(Benzo[d][1,3]dioxol-5-yl)-*N*-methylquinolinium trifluoromethanesulfonate (5b): orange micro needles (72 mg, 67 %). mp 147-149 °C. ^1H NMR (500 MHz, CDCl_3) δ 4.51 (s, 3H, NCH_3), 6.08 (s, 2H, CH_2), 6.99 (d, $J = 8.1$ Hz, 1H, aromatic H), 7.13 – 7.19 (m, 2H, aromatic H), 7.80 (d, $J = 8.4$ Hz, 1H, aromatic H), 7.87 (t, $J = 7.5$ Hz, 1H, aromatic H), 8.14 – 8.17 (m, 2H, aromatic H), 8.39 (d, $J = 9.3$ Hz, 1H, aromatic H), 8.81 (d, $J = 8.6$ Hz, 1H, aromatic H); ^{13}C NMR (125 MHz, CDCl_3) δ 42.9, 102.4, 109.4, 109.6, 119.7, 125.0, 125.2, 126.0, 128.6, 130.0, 130.3, 132.4, 136.4, 140.1, 145.8, 148.8, 151.1; HRMS

(FAB) calcd for $C_{17}H_{14}NO_2$ $[M - OTf]^+$ 264.1025, found 264.1006. Anal. Calcd for $C_{18}H_{14}F_3NO_5S$: C, 52.30; H, 3.41; N, 3.39. Found: C, 52.36; H, 3.64; N, 3.31.

6-Methoxy-2-(4-methoxyphenyl)-N-methylquinolinium trifluoromethanesulfonate (5c): pale yellow crystals (90 mg, 81 %). mp 164-166 °C. 1H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.48 (s, 3H, NCH_3), 7.10 (d, $J = 8.6$ Hz, 2H, aromatic H), 7.47 (d, $J = 2.6$ Hz, 1H, aromatic H), 7.60 (d, $J = 8.6$ Hz, 2H, aromatic H), 7.70 – 7.75 (m, 2H, aromatic H), 8.30 (d, $J = 9.5$ Hz, 1H, aromatic H), 8.79 (d, $J = 8.6$ Hz, 1H, aromatic H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.8, 55.7, 56.4, 107.9, 115.1, 120.9, 124.5, 125.2, 128.4, 130.4, 131.6, 131.7, 144.4, 156.8, 159.8, 162.4; HRMS (FAB) calcd for $C_{18}H_{18}NO_2$ $[M - OTf]^+$ 280.1338, found 280.1345. Anal. Calcd for $C_{19}H_{18}F_3NO_5S$: C, 53.14; H, 4.23; N, 3.26. Found: C, 53.01; H, 4.32; N, 3.14.

General procedure for the synthesis of 1a – 1c. To a stirred solution of **5** (0.030 mmol) in NaOH aq. (0.5 mL, 2.0 wt %) was added $K_3[Fe(CN)_6]$ (0.090 mmol) and the resulting solution was stirred for 12 h at rt. The reaction mixture was washed with brine and extracted with CH_2Cl_2 . The organic layer was dried over $MgSO_4$. Removal of the solvent *in vacuo*, followed by chromatography on silica gel column (MeOH / $CHCl_3 = 1 / 99$), afforded **1**.

Eduleine (1a): colorless crystals (from $CHCl_3$ / AcOEt, 5 mg, 63 %). mp 186-188 °C (lit.,⁶ 183-186 °C). 1H NMR (500 MHz, $CDCl_3$) δ 3.55 (s, 3H, NCH_3), 3.89 (s, 3H, OCH_3), 6.22 (s, 1H, 3-H), 7.27 (dd, $J = 9.3, 3.1$ Hz, 1H aromatic H), 7.34 – 7.36 (m, 2H, aromatic H), 7.43 – 7.45 (m, 5H, aromatic H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.3, 55.8, 105.3, 111.8, 117.6, 122.9, 128.1, 128.6, 128.8, 129.5, 135.9, 136.6, 135.8, 156.3, 176.9; HRMS (FAB) calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1181, found 266.1182.

Graveoline (1b): white solid (from $CHCl_3$ / AcOEt, 3 mg, 32 %). mp 198-200 °C (lit.,⁶ 204-205 °C). 1H NMR (500 MHz, $CDCl_3$) δ 3.63 (s, 3H, NCH_3), 6.07 (s, 2H, CH_2), 6.28 (s, 1H, 3-H), 6.86 (s, 1H, aromatic H), 6.89 – 6.93 (m, 2H, aromatic H), 7.41 (t, $J = 7.5$ Hz, 1H, aromatic H), 7.54 (d, $J = 8.6$ Hz, 1H, aromatic H), 7.69 – 7.71 (m, 1H, aromatic H), 8.48 (d, $J = 8.1$ Hz, 1H, aromatic H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.2, 101.7, 108.6, 109.0, 112.7, 115.9, 122.7, 123.6, 126.7, 126.9, 129.5, 132.3, 142.0, 147.9, 148.7, 154.3, 177.6; HRMS (FAB) calcd for $C_{17}H_{14}NO_3$ $[M + H]^+$ 280.0974, found 280.0967. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.06; H, 5.16; N, 5.07.

6-Methoxy-2-(4-methoxyphenyl)-1-methylquinolin-4(1H)-one (1c): white solid (from $CHCl_3$ / AcOEt, 2 mg, 23 %). mp 208-210 °C. 1H NMR (500 MHz, $CDCl_3$) δ 3.57 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3),

3.89 (s, 3H, OCH₃), 6.22 (s, 1H, 3-H), 6.94 (d, *J* = 8.8 Hz, 2H, aromatic H), 7.25 – 7.29 (m, 3H, aromatic H), 7.43 (d, *J* = 9.3 Hz, 1H, aromatic H), 7.84 (d, *J* = 3.1 Hz, 1H, aromatic H); ¹³C NMR (125 MHz, CDCl₃) δ 37.4 (s, NCH₃), 55.4, 55.9, 100.5, 105.8, 106.7, 111.8, 114.1, 117.7, 122.8, 126.5, 128.2, 130.1, 156.2, 160.5, 170.9; HRMS (FAB) calcd for C₁₈H₁₈NO₃ [M + H]⁺ 296.1287, found 296.1308.

ACKNOWLEDGEMENTS

This work was supported by a grant-in-aid for Initiatives for Attractive Education for Graduate Schools (No. b043) from the Ministry of Education, Culture, Sports, Science and Technology and Waseda University Grant for Special Research Projects (No. 2004A-152 and 2005B-157). T. N. is indebted by the Grant-in-aid for Young Scientist (B) (No. 18750053) from the Ministry of Education, Culture, Sports, and Science.

REFERENCES

1. a) F. A. Kincl, J. Romo, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, **1956**, 4163. b) D. R. Boyd, and M. F. Grundon, *J. Chem. Soc.*, **1970**, 556. c) S. Funayama, R. Tanaka, Y. Kumekawa, T. Noshita, T. Mori, T. Kashiwagura, and K. Murata, *Biol. Pharm. Bull.*, 2001, **24**, 100.
2. a) H. R. Arthur and H. T. Cheung, *Aust. J. Chem.*, 1960, **13**, 510. b) A. M. Hale, K. M. Meepagala, A. Oliva, G. Aliotta, and S. O. Duke, *J. Agric. Food. Chem.*, 2004, **52**, 3345.
3. a) C. Pain, S. Celanire, G. Guillaumet, and B. Joseph, *Tetrahedron*, 2003, **59**, 9627. b) Y.-Y. Lai, L.-J. Huang, K.-H. Lee, Z. Xiao, K. F. Bastow, T. Yamori, S.-C. Kuo, *Bioorg. Med. Chem.*, 2005, **13**, 265. c) F. Van Bambeke, J. -M. Michot, J. Van Eldere, and P. M. Tulkens, *Clinical Microbiology and Infection*, 2005, **11**, 256. d) S.-C. Kuo, H.-Z. Lee, J.-P. Juang, Y.-T. Lin, T.-S. Wu, J.-J. Chang, D. Lednicer, K. D. Paull, C. M. Lin, E. Hamel, and K.-H. Lee, *J. Med. Chem.*, 1993, **36**, 1146. e) L. Li, H.-K. Wang, S.-C. Kuo, T.-S. Wu, D. Lednicer, C. M. Lin, E. Hamel, and K.-H. Lee, *J. Med. Chem.*, 1994, **37**, 1126.
4. a) L. Limpach, *Ber. Dtsch. Chem. Ges.*, 1931, **64**, 970. b) N. D. Heindel, I. S. Bechara, P. D. Kennewell, J. Molnar, C. J. Ohnmacht, S. M. Lemke, and T. F. Lemke, *J. Med. Chem.*, 1968, **11**, 1218.
5. a) R. J. Chong, M. A. Siddiqui, and V. Snieckus, *Tetrahedron Lett.*, 1986, **27**, 5323. b) B. C. Chen, X. Huang, and J. Wang, *Synthesis*, **1987**, 482. c) R. Annunziata, G. Palmisano, and S. Tpollari, *Synth. Commun.*, 1996, **26**, 495.
6. J. Koyama, I. Toyokuni, and K. Tagahara, *Chem. Pharm. Bull.*, 1999, **47**, 1038.
7. B. M. Adger, S. Bradbury, M. Keating, C. W. Rees, R. C. Storr, and M. T. Williams, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 31.

8. T. Nakajima, T. Inada, T. Igarashi, T. Sekioka, and I. Shimizu, *Bull. Chem. Soc. Jpn.*, 2006, to be published.