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 IRIDIUM-CATALYZED THREE-COMPONENT COUPLING QUINOLINE SYNTHESIS

Takayuki Nakajima, Takashi Inada, and Isao Shimizu*

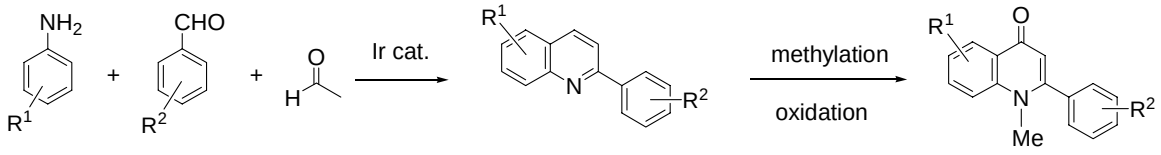
Department of Applied Chemistry, Graduate School of Science and Engineering, Waseda University, Okubo 3-4-1, Shinjuku-ku, Tokyo 169-8555, Japan.E-mail:shimizui@waseda.jp

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 trifrate followed by oxidation with potassium ferricianate 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

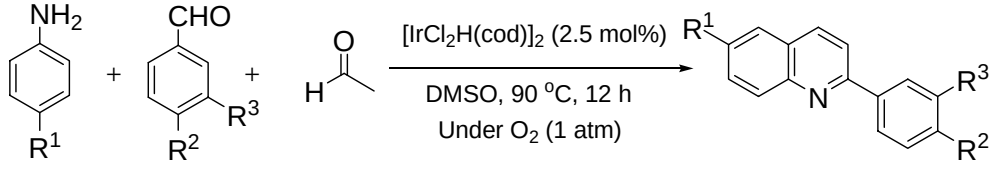
iridium-catalyzed three component coupling reaction,[8] which provides a facile synthesis of 2-aryl-4-quinolones as shown in the following Scheme 1.



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

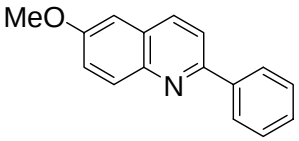
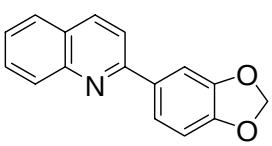
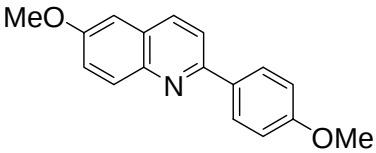
RESULTS AND DISCUSSION

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 = OMe), benzaldehyde (**3a**), and acetaldehyde was carried out in the presence of a catalytic amount of the iridium complex, $[IrCl_2H(cod)]_2$, in DMSO under oxygen atmospheres at 90 ^oC 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.



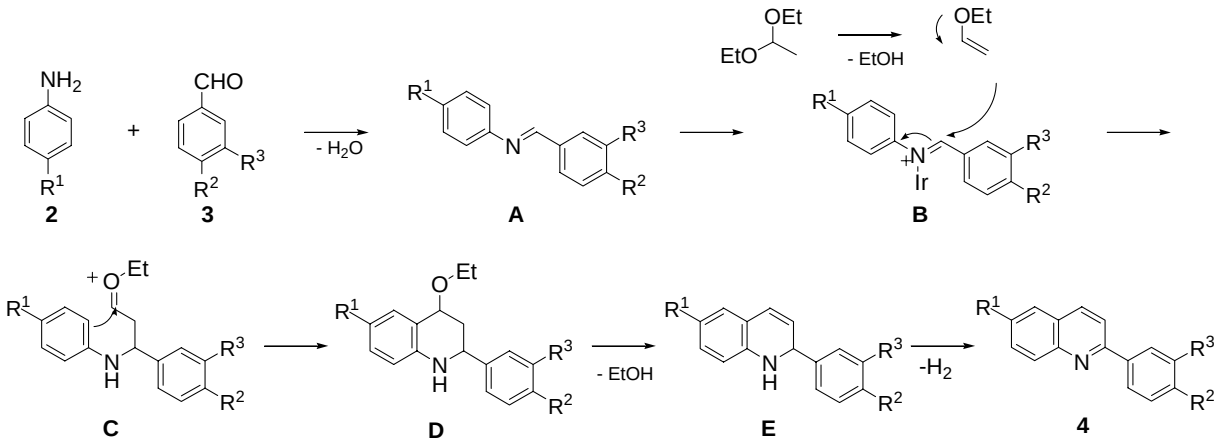
2 **3** **4**

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]

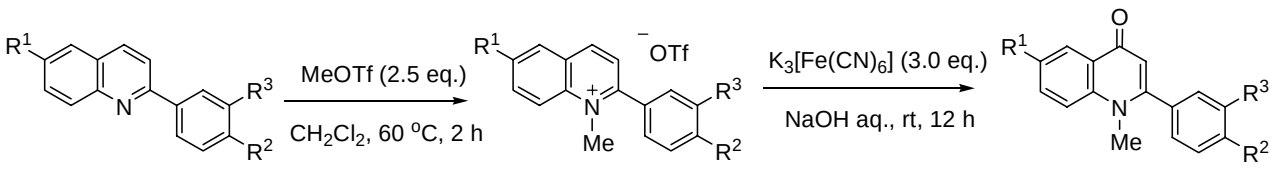
a) Isolated yield based on arylamine (**2**). b) 1,1-Dimethoxyethane was used, instead of acetaldehyde.

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.



4a (R^1 = MeO, R^2 = R^3 = H)
4b (R^1 = H, R^2+R^3 = OCH_2O)
4c (R^1 = R^2 = MeO, R^3 =H)

5a (80%)
5b (67%)
5c (81%)

1a (63%)
1b (32%)
1c (23%)

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 °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 ferricianate 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

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ 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 $[IrCl_2H(cod)]_2$ (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 ºC 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 $MgSO_4$. 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 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.5 (s, OCH_3), 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 $C_{16}H_{14}NO$ $[M + H]^+$ 236.1075, found 236.1086. Anal. Calcd for $C_{16}H_{13}NO$: 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 ^{o}C (lit.,[6] 95-96 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 2H, CH_2), 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 $C_{16}H_{12}NO_2$ $[M + H]^+$ 250.0868, found 250.0884.

6-Methoxy-2-(4-methoxyphenyl)quinoline (4c): colorless crystals (from AcOEt / hexane, 34 mg, 13 %). mp 128-131 °C. ^{1}H 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 $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1181, found 266.1163. Anal. Calcd for $C_{17}H_{15}NO_2$: 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 ºC. 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. ^{1}H 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 $C_{17}H_{16}NO$ $[M – OTf]^+$ 250.1226, found 250.1226. Anal. Calcd for $C_{18}H_{16}F_3NO_4S$: 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. ^{1}H 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. ^{1}H 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**.

Eduline (1a): colorless crystals (from $CHCl_3$ / AcOEt, 5 mg, 63 %). mp 186-188 °C (lit.,[6] 183-186 °C). ^{1}H 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). ^{1}H 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(1*H*)-one (1c): white solid (from $CHCl_3$ / AcOEt, 2 mg, 23 %). mp 208-210 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3),

3.89 (s, 3H, OCH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.4 (s, NCH_3), 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 $C_{18}H_{18}NO_3$ $[M + H]^+$ 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.