DOI 10.5012/bkcs.2011.32.1.153

Concise Synthesis of (±)-Rhinacanthin A, Dehydro α-Lapachone, and β-Lapachone, and Pyranonaphthoquinone Derivatives

Xue Wang, Ye Chen, and Yong Rok Lee*

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea
**E-mail: yrlee@yu.ac.kr*
Received September 29, 2010, Accepted November 5, 2010

A concise synthesis of (±)-rhinacanthin A is achieved in two steps by epoxidation of dehydro-α-lapachone, followed by chemo- and regioselective reduction. Dehydro-α-lapachone was also synthesized in two steps starting from 4-methoxy-1-naphthol by ethylenediamine diaetate (EDDA)-catalyzed benzopyran formation and a CAN-mediated oxidation reaction. β-Lapachone was synthesized in three steps from 4-methoxy-1-naphthol by benzopyran formation, catalytic hydrogenation, and Jones oxidation. As additional reactions, synthesis of pyranonaphthoquinone derivatives with the pyranokunthone B skeleton has been achieved in a single step from readily available 2-hydroxy-6-methoxy-1,4-naphthoquinone and 2-hydroxy-7-methoxy-1,4-naphthoquinone.

Key Words: Pyranonaphthoquinones, Rhinacanthin A, Dehydro-α-lapachone, β-Lapachone

Introduction

Pyranonaphthoquinones are widely distributed throughout nature and play important physiological roles in animals and plants.[1] Among these, dehydro-α-lapachone (**1**) and α-lapachone (**2**), containing a 1,4-naphthoquinone moiety, are primarily isolated from *Catalpa ovata* and *Tabebuia avellanedae* (Fig. 1).[2] Rhinacanthin A (**3**) is isolated from *Rhinacanthus nastus*, which is found in China and India.[3] Dehydro-β-lapachone (**4**) and β-lapachone (**5**), bearing a 1,2-naphthoquinone skeleton, are isolated from *Austroplenckia populnea* and *Tabebuia avellanedae*.[4] They possess antibacterial, antifungal, antitrypanosomal, antimalarial, and antitumor activities and are used in traditional medicines in Japan and China for the treatment of pyrexia, jaundice, and edema by nephritis.[5] Selected biological properties include reduction of HIV-1 replication, suppression of both acute and chronic infections, inhibition of DNA topoisomerase I, induction of chromosomal alterations, inhibition of reverse transcriptase and DNA polymerase-α, and blockade of activation of NF-*k*B and AP-1.[6-12] They also have potential clinical utility in the treatment of human leukemia and prostate cancer.[13-14] In particular, combination of β-lapachone (**5**) and taxol is combined synergistically to induce cell death in many types of human carcinoma cells, including ovarian, breast, prostate, lung, melanoma, colon, and pancreatic.[15] β-Lapachone (**5**) has been investigated for the treatment of specific cancers associated with elevated NQO1 levels[16] and is currently in phase II clinical trials for the treatment of pancreatic cancer.[17] Pyranokunthone A (**6**) and B (**7**), with a 1,4-naphtoquinone skeleton, are isolated from the root bark extract of *Stereospermum kunthianum*.[18] They have been used as valuable remedies for the treatment of fever in Uganda and have also shown strong antimalarial activity.[18] This range of important biological activities and properties has stimulated further research interest into the synthesis of natural and unnatural pyranonaphthoquinone derivatives.

This lab has already developed a methodology for the synthesis of biologically interesting pyranonaphthoquinone derivatives, including dehydro-α-lapachone (**1**) and α-lapachone (**2**), starting from 2-hydroxy-1,4-naphthoquinone (**8**) through ethylenediamine diacetate (EDDA)-catalyzed domino Knoevenagel condensation/6π-electrocyclization followed by hydrogenation (Scheme 1).[19] As part of an ongoing study of the synthetic efficacy of this methodology, further reactions for the synthesis of natural and unnatural pyranonaphthoquinone derivatives were examined.

Recently, utilizing this methodology as a key step, novel pyranonaphthoquinone inhibitors of indoleamine 2,3-dioxygenase as an important new therapeutic target for the treatment of cancer have been developed by Malachowski.[20] Due to this importance of pyranonaphthoquinones, synthesis of (±)-rhinacanthin A (**3**) was first attempted using dehydro-α-lapachone (**1**). Although the total synthesis of rhinacanthin A (**3**), as both racemic

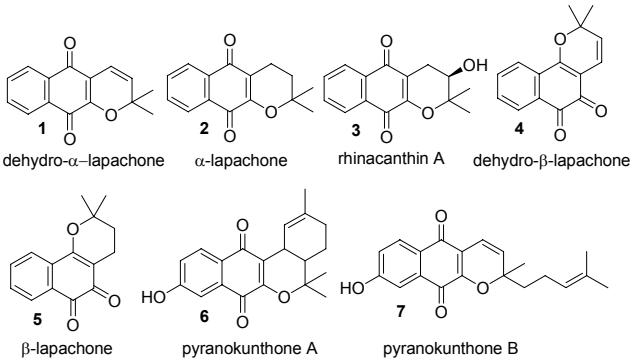
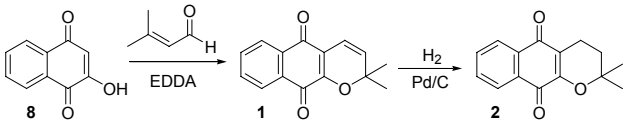
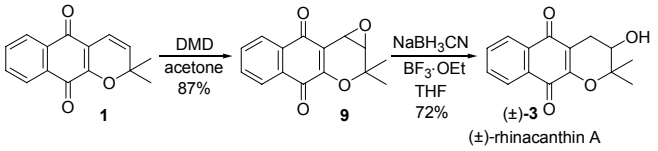


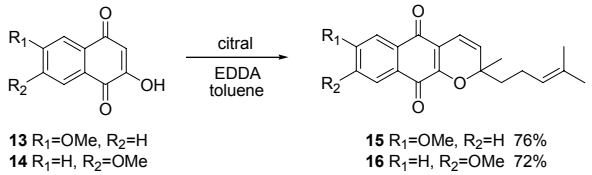
Figure 1



Scheme 1



Scheme 2

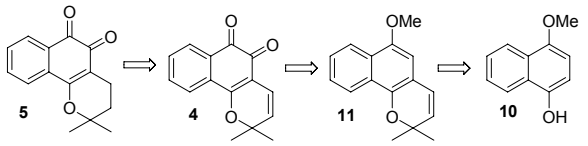


Scheme 5

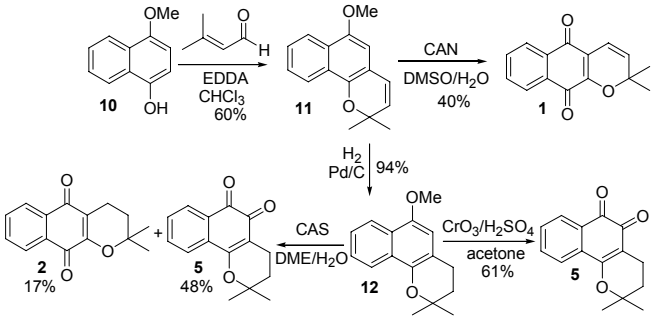
and enantioenriched products, was respectively achieved in 7 and 8 steps,[21] simple and more concise synthetic approaches are still required. Reaction of **1** with dimethyldioxirane in acetone afforded epoxide **9** in 87%, which was then reduced with $NaBH_3CN$ in the presence of BF_3·OEt in THF to give (±)-**3** in 72% yield with chemo- and regioselectivity (Scheme 2).[22] The spectral data of synthetic material **3** were in good agreement with those reported in the literature.[21]

In view of the great importance of β-lapachone (**5**), a number of synthetic methods have been reported.[23] The best method for the preparation of **5** is the sulfuric acid-catalyzed cyclization of lapachol.[23b] However, this method provided both α-lapachone (**2**) and β-lapachone (**5**) in 34 and 39% yields, respectively. Another method has employed microwave irradiation of lapachol in the presence of montmorillonite clay K 10 to give **2** and **5** as a mixture in 70 and 10% yields, respectively.[23c] In particular, lapachol has been synthesized from 2-hydroxy-1,4-naphthoquinone through base-mediated alkylation with prenyl bromide. However, this method has a limitation of very low product yield due to formation of the *O*-alkylation product as a major component.[24] Thus, more efficient and effective routes for their syntheses are still in demand. As shown in Scheme 3, we speculate that β-lapachone (**5**) could be prepared from dehydro-β-lapachone (**4**) by catalytic hydrogenation. Compound **4** could be synthesized by oxidation of lapachenole (**11**), generated from commercially available 4-methoxy-1-naphthol (**10**) through a benzopyran formation reaction.

As shown in Scheme 4, treatment of **10** with 3-methyl-2-butenal in the presence of 20 mol % of ethylenediamine diacetate in refluxing chloroform gave lapachenole (**11**) in 60% yield, a natural product isolated from *Tabebuia chrysantha*.[25] For conversion to dehydro-β-lapachone (**4**), reaction of **11** with ceric ammonium nitrate in aqueous DMSO was carried out, but the unexpected dehydro-α-lapachone (**1**) was produced in 40% yield through oxidation and rearrangement.[26] The structure of synthetic material **1** was confirmed by comparison with reported data.[19,20] To synthesize β-lapachone (**5**), other reactions were attempted. Catalytic hydrogenation of **11** over Pd/C (20 psi) in ethyl acetate for 1 h gave **12** in 94% yield. Oxidation of **12** with ceric ammonium sulfate (CAS) in aqueous DME afforded both **2** and **5** in 17 and 48% yields, whereas with the Jones reagent, **5** was produced in 61% yield. Compounds **2** and **5** were separated by column chromatography and assigned by comparison with reported data.[23b]



Scheme 3



Scheme 4

Finally, to synthesize the pyranokunthone B derivatives, additional reactions of 2-hydroxy-6-methoxy-1,4-naphthoquinone (**13**) and 2-hydroxy-7-methoxy-1,4-naphthoquinone (**14**) were carried out (Scheme 5). Treatment of **13** and **14** with citral, in the presence of ethylenediamine diacetate in refluxing toluene for 8 h, provided cycloadducts **15** and **16** with pyranokunthone B skeleton in 76 and 72% yields, respectively.

In conclusion, concise synthesis of (±)-rhinacanthin A (**3**) was achieved in two steps from dehydro-α-lapachone (**1**) by epoxidation followed by chemo- and regioselective reduction. Dehydro-α-lapachone (**1**) was synthesized in two steps from 4-methoxy-1-naphthol (**10**) by EDDA-catalyzed benzopyran formation and CAN-mediated oxidation. β-Lapachone (**5**) was accomplished in three steps by EDDA-catalyzed benzopyran formation, catalytic reduction, and Jones oxidation reaction from **10**. The synthesis of pyranonaphthoquinone derivatives with the pyranokunthone B skeleton has been achieved in a single step from readily available 2-hydroxy-6-methoxy-1,4-naphthoquinone and 2-hydroxy-7-methoxy-1,4-naphthoquinone.

Experimental

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined in capillary tubes on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS mass spectra were carried out by Korea Basic Science Institute.

2,2-Dimethyl-3,4-epoxy-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (9). A stirred mixture of **1** (0.5 g, 2.1 mmol) in acetone (10 mL) was treated with 25 mL of dimethyldioxirane (0.09 M in acetone) at room temperature for 4 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel using hexane/ethyl acetate (5:1) afforded **9** (0.464 g, 87%) as a solid: mp 139 - 140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.07 (2H, m), 7.76-7.65 (2H, m), 4.33 (1H, d, J = 4.4 Hz), 3.52 (1H, d, J = 4.4 Hz), 1.68 (3H, s), 1.43 (3H, s); IR (KBr): 2987, 2936, 1682, 1651, 1618, 1595, 1578, 1435, 139 9, 1341, 1314, 1277, 1211, 1154, 1086, 965, 851, 725 cm^{-1}; HRMS: m/z (M^+) calcd for $C_{15}H_{12}O_4$: 256.0736. Found: 256.0738.

(±)-Rhinacanthin A (3).[21] BF_3·Et_2O (0.3 mL) was added dropwise to a stirred solution of **9** (0.256 g, 1.0 mmol) and sodium cyanoborohydride (0.075 g, 1.2 mmol) in THF (20 mL) at room temperature. After 1 h reaction was quenched with water (50 mL) and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with water (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography on silica gel using hexane/ethyl acetate (3:1) afforded **3** (0.186 g, 72%) as a solid: mp 193 - 194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.03 (2H, m), 7.71-7.62 (2H, m), 3.87 (1H, t, J = 5.1 Hz), 2.85 (1H, dd, J = 18.8, 5.1 Hz), 2.67 (1H, dd, J = 18.8, 5.1 Hz), 1.89 (1H, br s), 1.46 (3H, s), 1.41 (3H, s); IR (KBr) 3522, 2926, 1651, 1618, 1373, 1342, 1309, 1269, 1207, 1130, 1084, 966, 796, 725 cm^{-1}.

Lapachenole (11). 4-Methoxy-1-naphthol (**10**) (0.174 g, 1.0 mmol) and 3-methyl-2-butenal (0.168 g, 2.0 mmol) were dissolved in $CHCl_3$ (10 mL) and ethylenediamine diacetate (36 mg, 0.2 mmol) was added at room temperature. The mixture was refluxed for 24 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) to give **11** (0.144 g, 60%) as a solid: mp 63 - 64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25-8.22 (2H, m), 7.56-7.46 (2H, m), 6.54 (1H, s), 6.44 (1H, d, J = 9.6 Hz), 5.68 (1H, d, J = 9.6 Hz), 3.97 (3H, s) 1.57 (6H, s); IR (KBr) 3071, 3011, 2975, 2934, 1645, 1597, 1456, 1406, 1389, 1370, 1337, 1277, 1208, 1165, 1130, 1117, 1096, 1030, 997, 984, 953, 943, 901, 841, 819, 768, 748 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{16}O_2$: 240.1150. Found: 240.1152.

Dehydro-α-lapachone (1).[20b] To a solution of **11** (0.12 g, 0.5 mmol) in DMSO (10 mL) and H_2O (1 mL) was added ceric ammonium nitrate (1.645 g, 3.0 mmol) at room temperature and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched by addition of water (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated at reduced pressure. The removal of the solvent under reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (2:1) to give product **1** (0.048 g, 40%) as a solid: mp 145 - 146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.05 (2H, m), 7.70-7.64 (2H, m), 6.64 (1H, d, J = 10.0 Hz), 5.71 (1H, d, J = 10.0 Hz), 1.54 (6H, s); IR (KBr): 3079, 3017, 2976, 2922, 1676, 1647, 1593, 1570, 1416, 1331, 1275, 1211, 1190, 1134, 968, 947 cm^{-1}.

Dihydrolapachenole (12). To a solution of **11** (0.048 g, 0.2 mmol) in ethyl acetate (10 mL) in a Parr bottle was added 10% Pd/C (10 mg). The bottle was shaken for 1 h at 20 psi of H_2. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) to give **12** (0.046 g, 94%) as a solid: mp 77 - 78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.10 (2H, m), 7.50-7.33 (2H, m), 6.47 (1H, s), 3.93 (3H, s), 2.83 (2H, t, J = 6.7 Hz), 1.87 (2H, t, J = 6.7 Hz), 1.39 (6H, s); IR (KBr) 2930, 1634, 1599, 1458, 1387, 1318, 1273, 1206, 1157, 1121, 1100, 924, 768 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{18}O_2$: 242.1307. Found: 242.1306.

α-Lapachone (2) and β-Lapachone (5). To a solution of **12** (0.242 g, 1.0 mmol) in DME (5 mL) and H_2O (1 mL) was added ammonium cerium sulfate (1.404 g, 5.5 mmol) at room temperature and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched by addition of water (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with water (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure, and then purified by flash chromatography on silica gel using hexane/ethyl acetate (7:1) to afford **2** (0.042 g, 17%) and **5** (0.116 g, 48%). Compound **2**: mp 113 - 114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08-8.02 (2H, m), 7.70-7.62 (2H, m), 2.60 (2H, t, J = 6.6 Hz), 1.80 (2H, t, J = 6.6 Hz), 1.42 (6H, s); IR (KBr) 2974, 2948, 1682, 1638, 1613, 1578, 1391, 1341, 1310, 1273, 1208, 1119, 961 cm^{-1}. Compound **5**: mp 154 - 155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, d, J = 7.8 Hz), 7.76 (1H, d, J = 7.8 Hz), 7.59 (1H, dd, J = 7.8, 7.5 Hz), 7.45 (1H, dd, J = 7.8, 7.5 Hz), 2.51 (2H, t, J = 6.6 Hz), 1.80 (2H, t, J = 6.6 Hz), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 178.4, 162.0, 134.7, 132.5, 130.6, 130.1, 128.4, 124.0, 112.6, 79.2, 31.5, 26.7, 16.1; IR (KBr) 2970, 1693, 1630, 1581, 1457, 1388, 1308, 1293, 1165, 11123, 936, 830, 771 cm^{-1}.

β-Lapachone (5). To a solution of **12** (0.242 g, 1.0 mmol) in acetone (10 mL) was added Jones reagent (2 mL, 1 M/L, 2.0 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 4 h. The solvent was evaporated under reduced pressure. The removal of solvent left an oily residue which was purified by flash column chromatography on silica gel using hexane/ethyl acetate (7:1) to afford **5** (0.148 g, 61%) as a solid.

7-Methoxy-2-methyl-2-(4-methyl-pent-3-enyl)-2*H*-benzo[g]chromene-5,10-dione (15). To a solution of 2-hydroxy-6-methoxy-1,4-naphthoquinone (**13**) (0.204 g, 1.0 mmol) with citral (0.305 g, 2.0 mmol) in toluene (10 mL) was added ethylenediamine diacetate (0.036 g, 0.2 mmol) at room temperature. The mixture was refluxed for 8 h and then cooled to room temperature. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **15** (0.257 g, 76%) as a solid: mp 89 - 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 8.4 Hz), 7.46 (s, 1H), 7.06 (dd, 1H, J = 8.4, 2.4 Hz), 6.62 (d, 1H, J = 9.9 Hz), 5.33 (d, 1H, J = 9.9 Hz), 5.03 (t, 1H, J = 6.6 Hz), 3.88 (s, 3H), 2.13-2.03 (m, 2H), 1.95-1.85 (m, 1H), 1.68-1.60 (m, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 178.6, 164.2, 153.1, 133.7, 132.1, 128.9, 128.6, 124.8, 123.4, 119.0, 117.0, 115.9, 109.9, 83.0, 55.8, 41.5, 27.5, 25.5, 22.6, 17.6; IR (KBr) 2925, 1653, 1586, 1447, 1326, 1249, 1111, 971, 827, 827, 736 cm^{-1}; HRMS m/z (M^+) calcd for

$C_{21}H_{22}O_4$: 338.1518. Found: 338.1514.

8-Methoxy-2-methyl-2-(4-methyl-pent-3-enyl)-2*H*-benzo [g]chromene-5,10-dione (16). To a solution of 2-hydroxy-7-methoxy-1,4-naphthoquinone (**14**) (0.204 g, 1.0 mmol) with citral (0.305 g, 2.0 mmol) in toluene (10 mL) was added ethylenediamine diacetate (0.036 g, 0.2 mmol) at room temperature. The mixture was refluxed for 8 h and then cooled to room temperature. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **16** (0.244 g, 72%) as a solid; mp 59 - 60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 8.7 Hz), 7.47 (d, 1H, J = 2.7 Hz), 7.11 (dd, 1H, J = 8.7, 2.7 Hz), 6.64 (d, 1H, J = 9.9 Hz), 5.62 (d, 1H, J = 9.9 Hz), 5.04 (t, 1H, J = 6.3 Hz), 3.88 (s, 3H), 2.12-2.02 (m, 2H), 1.95-1.85 (m, 1H), 1.71-1.62 (m, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 179.6, 163.6, 152.4, 133.3, 132.1, 129.8, 128.4, 124.8, 123.4, 119.9, 117.3, 116.1, 109.9, 82.8, 55.8, 41.5, 27.4, 25.5, 22.6, 17.6; IR (KBr) 2962, 1674, 1644, 1586, 1440, 1408, 1344, 1317, 1282, 1201, 1166, 1109, 980, 912, 835, 734 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{22}O_4$: 338.1518. Found: 338.1517.

Acknowledgments. Following are results of a study on the "Human Resourse Development Center for Economic Region Leading Industry" Project, supported by the Minister of Education, Science & Technology (MEST) and the National Research Foundation of Korea (NRF).

References

1. Thomson, R. H. *Naturally Occurring Quinones III*, *Recent Advances*; Chapman and Hall: London, 1987; p 609.
2. (a) Cho, J. Y.; Kim, H. Y.; Choi, G. J.; Jang, K. S.; Lim, H. K.; Lim, C. H.; Cho, K. Y.; Kim, J.-C. *Pest Manag. Sci.* **2006**, *62*, 414. (b) Joshi, K. C. *Planta Med*. **1978**, *34*, 219. (c) Wurzburger, J.; Leshem, Y. *Phytochemistry* **1976**, *15*, 225. (d) Burnett, A. R.; Thomson, R. H. *J. Chem. Soc., C* **1967**, 2100.
3. Wu, T. S.; Tien, H. J.; Yeh, M. Y.; Lee, K. H. *Phytochemistry* **1988**, *27*, 3787.
4. (a) de Sousa, J. R.; Silva, G. D. F.; Miyakoshi, T.; Chen, C.-L. *J. Nat. Prod*. **2006**, *69*, 1225. (b)Woo, H. J.; Park, K.-Y.; Rhu, C.-H. Lee, W. H.; Choi, B. T.; Kim, G. Y.; Park, Y.-M.; Choi, Y. H. *J. Med. Food* **2006**, *9*, 161.
5. (a) Goncalves, A. M.; Vasconcellos, M. E.; Docampo, R.; Cruz, F. S.; De Souza, W.; Leon, W. *Mol. Biochem. Parasitol*. **1980**, *1*, 167. (b) Guiraud, P.; Steiman, R.; Campos-Takaki, G.-M.; Seigle-Murandi, F.; De Buochberg, M. S. *Planta. Med*. **1994**, *60*, 373.
6. Docampo, R.; Cruz, F. S.; Boveris, A.; Muniz, R. P. A.; Esquivel, D. M. S. *Biochem. Pharmacol*. **1979**, *28*, 723.
7. Boothman, D. A.; Pardee, A. B. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 4963.
8. Li, C. J.; Pardee, A. B. *Cancer Res*. **1995**, *55*, 3712.
9. Planchon, S. M.; Wuerzberger, S.; Frydman, B.; Witiak, D. T.; Hutson, P.; Church, D. R.; Wilding, G.; Bootman, D. A. *Cancer Res*. **1995**, *55*, 3706.
10. Li, C. J.; Zhang, L. J.; Dezube, B. J.; Grumpacker, C. J.; Pardee, A. B. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1839.
11. Schuerch, A. R.; Werrli, G. *Eur. J. Biochem*. **1978**, *84*, 197.
12. Manna, S. K.; Gad, Y. P.; Mukhopadhyay, A.; Aggarwal, B. B. *Biochem. Pharmacol.* **1999**, *57*, 763.
13. Villamil, S. H. F.; Perissimoti, L. J.; Stoppani, A. O. M. *Biochem. Pharmacol.* **1996**, *52*, 1875.
14. Frydman, B.; Marton, I. J.; Sun, J. S.; Nedi, K.; Witiak, D. T.; Liu, A. A. *Cancer Res.* **1997**, *57*, 620.
15. Li, C. J.; Li, Y. Z.; Pinto, A. V.; Pardee, A. B. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 13369.
16. (a) Ough, M.; Lewis, A.; Bey, E. A.; Gao, J.; Ritchie, J. M.; Bornmann, W. G.; Boothman, D. A.; Oberley, L. W.; Cullen, J. J. *Cancer Biol. Ther*. **2005**, *4*, 95. (b) Bey, E. A.; Bentle, M. S.; Reinicke, K. E.; Dong, Y.; Yang, C. R.; Girard, L.: Minna, J. D.; Bornmann, W. G.; Gao, J.; Boothman, D. A. *Proc. Natl. Acad. Sci. U S A* **2007**, *104*, 11832.
17. Bentle, M. S.; Bey, E. A.; Dong, Y.; Reinicke, K. E.; Boothman, D. A. *J. Mol. Histol*. **2006**, *37*, 203.
18. Onegi, B.; Kraft, C.; Köhler, I.; Freund, M.; Jenett-Siems, K.; Siems, K.; Beyer, G.; Melzig, M. F.; Bienzle, U.; Eich, E. *Phytochemistry* **2002**, *60*, 39.
19. (a) Lee, Y. R.; Lee, W. K. *Synth. Commun*. **2004**, *34*, 4537. (b) Lee, Y. R.; Choi, J. H.; Trinh, D. T. L.; Kim, N. W. *Synthesis* **2005**, 3026.
20. (a) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem*. **2008**, *51*, 1706. (b) Nasiri, H. R.; Bolte, M.; Schwalbe, H. *Nat. Prod. Res*. **2008**, *22*, 1225.
21. Kimachi, T.; Torii, E.; Ishimoto, R.; Sakue, A.; Ju-ichi, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1683.
22. (a) Taber, D. F.; Houze, J. B. *J. Org. Chem*. **1994**, *59*, 4004. (b) Chochrek, P.; Wicha, J. *Org. Lett*. **2006**, *8*, 2551.
23. (a) Amaral, A. C. F.; Barnes, R. A. *J. Heterocycl. Chem*. **1992**, *29*, 1457. (b) Perez-Sacau, E.; Estevez-Braun, A.; ravelo, A.; Ferro, E.; Tokuda, H.; Mukainaka, T.; Nishino, H. *Bioorg. Med. Chem*. **2003**, *11*, 483. (c) Singh, P.; Natani, K.; Jain, S.; Arya, K.; Dandia, A. *Nat. Prod. Res*. **2006**, *20*, 207.
24. Sun, J.; Geiser, A. H.; Frydman, B. *Tetrahedron Lett*. **1998**, *39*, 8221.
25. Burnett, A. R.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 850.
26. Alves, G. B. C.; Lopes, R. S. C.; Lopes, C. C.; Snieckus, V. *Synthesis* **1999**, 1875.