Bioorganic & Medicinal Chemistry Letters 20 (2010) 2086–2089

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Efficient microwave-assisted prenylation of pinostrobin and biological evaluation of its derivatives as antitumor agents

Hadi Poerwono [a], Shigeru Sasaki [b], Yoshiyuki Hattori [b], Kimio Higashiyama [b,*]

[a] Faculty of Pharmacy, Airlangga University, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia
[b] Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

ARTICLE INFO

Article history:
Received 15 January 2010
Revised 13 February 2010
Accepted 17 February 2010
Available online 20 February 2010

Keywords:
5-Hydroxy-7-methoxyflavanone
Prenylation
Microwave-assisted reaction
Mitsunobu reaction
Claisen rearrangement
Cross-metathesis
Anticancer activity

ABSTRACT

Pinostrobin (5-hydroxy-7-methoxyflavanone) obtained in relatively large amounts from fingerroot (*Boesenbergia pandurata*) was converted to its C-6 and C-8 prenylated derivatives. The Mitsunobu reaction, europium(III)-catalyzed Claisen–Cope rearrangement, and Claisen reaction coupled with cross-metathesis were used as the key steps. Using a sealed-vessel microwave reactor, the Mitsunobu and Claisen/Cope reactions occurred smoothly with short reaction times and in satisfactory yields. The target compounds and five new intermediary substances showed cytotoxic activity toward SK-BR-3, MCF-7, PC-3, and Colo-320DM human tumor cell lines, and all of them had significantly lower IC_{50} (μM) values than pinostrobin.

Flavonoids, including flavones, flavanones, flavanols, flavonols, and isoflavones, constitute the largest and most important group of polyphenolic compounds in plants. Erdtman reported the presence of a new flavonoid named pinostrobin (**1**, Fig. 1) in the heartwood of pine (*Pinus strobus*) about 65 years ago.[1] Since then, there have been about 300 articles that have included this flavanone as their subject. Besides its occurrence in plants belonging to Pinaceae,[2] pinostrobin has also been found in the following families: Fabaceae,[3] Asteraceae,[4] Salicaceae,[5] Lauraceae,[6] Zingiberaceae,[7] Piperaceae,[8] Chloranthaceae,[9] Myrtaceae,[10] Rosaceae,[11] Pteridaceae,[12] Annonaceae,[13] Lamiaceae,[14] Betulaceae,[15] Juglandaceae,[16] Polygonaceae,[17] Santalaceae,[18] Myricaceae,[19] Muntingiaceae,[20] Chenopodiaceae,[21] Grossulariaceae,[22] Notophagaceae,[23] Melianthaceae,[24] Acrobolbaceae (liverwort),[25] and propolis.[26]

Pinostrobin has been the subject of a number of studies on its bioactivities including cytotoxicity,[27] quinone reductase induction,[28] antioxidant activity,[29] antimicrobial activity,[30] virus protease inhibition,[31] antinociceptive activity,[32] anti-inflammatory activity,[33] and gastroprotective activity.[34] Moreover, Sukardiman et al. have suggested that the cytotoxicity of pinostrobin against human mammary carcinoma emerged from its inhibition of DNA Topoisomerase I activity.[35] In line with the above result, Le Bail et al. have confirmed that pinostrobin exhibited antiaromatase activity and decreased MCF-7 human breast cancer cell growth induced by dehydroepiandrosterone sulfate and estradiol.[36] In comparison with other prominent flavonoids found in honey, pinostrobin has been shown to be the most potent inducer of mammalian phase II chemoprotective and antioxidant enzymes as a result of an examination conducted by Fahey and co-workers.[37] As we have done in this study, this group has also suggested using the edible rhizomes of fingerroot (*B. pandurata*) as the most promising source of pinostrobin.

Furthermore, it has been suggested that prenylated flavonoids exhibit stronger bioactivities than those without prenyl substituents as assessed by the cAMP phosphodiesterase inhibition test, a useful tool for screening biologically active compounds contained in medicinal plants. The aforementioned test revealed that the

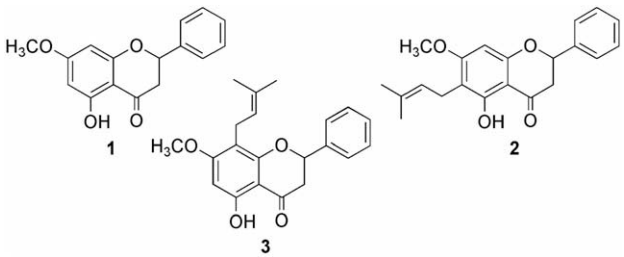


Figure 1. Pinostrobin (**1**) and its prenylated derivatives (**2** and **3**).

* Corresponding author.
E-mail address: kimio@hoshi.ac.jp (K. Higashiyama).

0960-894X/$ - see front matter Crown Copyright © 2010 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.02.068

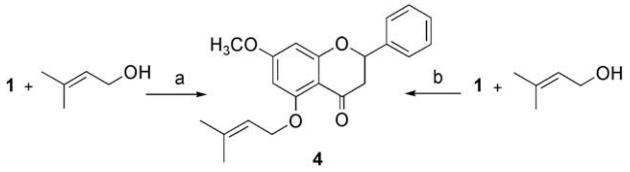
IC_{50} value of 8-prenylpinostrobin (**3**) was about one-sixth of that of pinostrobin (**1**).[38] More than a dozen years later, a group spanning seven universities found that flavanones bearing a hydrophobic prenyl, geranyl, or lavandulyl group at position 8 (in the A ring) were shown to be the strongest multi-drug resistance protein 1 (MRP1)/ATP-binding cassette C1 (ABCC1) inhibitors in a study of flavonoids as multi-drug resistance modifiers.[39] These findings have been ascertained by the very recent study conducted by Kadota and co-workers reporting that an increase of prenyl groups is one of the structural requirements for enhancing the cytotoxicity of flavanone derivatives.[40]

The considerable and extensive interest in pinostrobin and its prenylated derivatives has consequently led us to subject pinostrobin to a prenylation procedure yielding 6-prenylpinostrobin (**2**, Fig. 1) and 8-prenylpinostrobin (**3**, Fig. 1). Both the prenyl derivatives are known as naturally occurring flavonoids. In 1980, three different groups almost concurrently reported flavanone **3** as a new compound isolated from *Tephrosia* sp. (Fabaceae).[41] While there are a number of articles referring to C-8 prenylflavanone **3**,[42] there is only one report on the occurrence of C-6 prenylated congener **2** in a plant (*Derris rariflora*, Fabaceae).[43] Claisen rearrangement, which is known as a useful method for regioselective prenylation of phenolic natural products,[44] was used to synthesize the target compounds.

Hence, we embarked on synthesizing prenylflavanones **2** and **3** from flavanone **1**, which was isolated from the rhizomes of temu kunci (*B. pandurata*) grown in the East Java area of Indonesia. As outlined in Scheme 1, the already existing 7-*O*-methyl functionality of **1** serves favorably as a protective group. This sets the stage for installing the requisite C-5 prenyl ether moiety, which will be used as the substrate for the Claisen reaction. By using the Mitsunobu reaction, the condensation of flavanone **1** and 3-methyl-2-buten-1-ol in the presence of triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD) in dry tetrahydrofuran (THF) gave the desired 5-*O*-prenylflavanone **4** in 81% yield after a reaction time of 18 h. The yield was in agreement with previous studies reporting a similar O-prenylation of flavonoids using the classical Mitsunobu procedure.[45] The challenge of achieving both a shorter reaction time and a higher yield could, however, be fulfilled by heating the chemical reactions with microwave (MW) energy. Compared with conventional heating methods, microwave heating has been shown to dramatically decrease reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions.[46] A microwave-assisted Mitsunobu reaction is reliable, as it has been employed by previous groups to synthesize target molecules in satisfactory yields.[47] Therefore, flavanone **1**, and three equivalents of prenyl alcohol, Ph_3P, and diisoproyl azodicarboxylate (DIAD) were heated in dry THF in a sealed tube at 60 °C inside a microwave reactor (Scheme 1). This resulted in the C-5 prenylated flavanone **4** in 96% yield after a reaction time of just 30 min—a considerably higher percentage yield in a shorter reaction time than previously achieved.

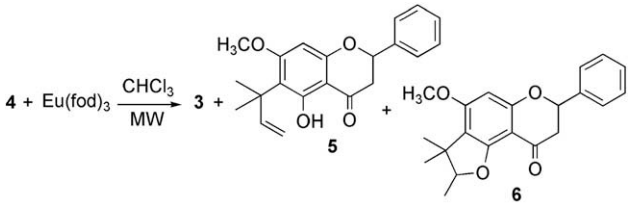
Once the prenyl ether intermediate **4** was available, attention was focused on C-prenylation at positions 6 or 8 of the flavanone depending on the conditions of Claisen rearrangement. Instead of using the conventional uncatalyzed condition in high boiling point solvents, we treated flavanone **4** with catalytic amounts (10 mol %) of $Eu(fod)_3$ in dry chloroform[48] at 60 °C for 12 h to give 6-(1,1-dimethylallyl)pinostrobin (**5**) as the sole product. As reported by other groups, however, similar reaction conditions of the Claisen procedure have been applied to 7,4′-diacetoxy-5-prenyloxyflavanone, 7,4′-diacetoxy-5-prenyloxyisoflavone, and 7,4′-diacetoxy-5-prenyloxyflavone, respectively, to give mainly the 8-prenylated derivatives along with minor *ortho*-rearranged products.[45] The predominance of *para*-rearranged products of the three 5-prenyloxyflavonoids suggests that a low temperature Claisen–Cope procedure using $Eu(fod)_3$ as the catalyst proceeds with high selectivity. This was, of course, contrary to the results of our study. A plausible source of the discrepancy is the electronic nature of the *meta*-substituents of phenolic substrates. It has been reported that electron-withdrawing groups, including $-OCOCH_3$, promote rearrangement to the *ortho* position next to the group, while electron-donating groups, including $-OCH_3$, have the opposite effect.[49]

In order to convert the regioselectivity for C–O into that for C–C, we attempted a microwave-assisted Claisen–Cope reaction catalyzed by $Eu(fod)_3$. To our knowledge, there is only one report to date that has employed europium(III)-catalyzed sigmatropic rearrangement under microwave heating,[50] and no report of such a reaction applied to the construction of *C*-prenyl flavonoids. Table 1 lists the details of our novel and facile procedure for synthesizing 8-prenylflavanone **3** via a lanthanide-catalyzed Claisen–Cope process of 5-*O*-prenylflavanone **4** under microwave irradiation. Initially, reacting prenyl ether **4** with 10 mol % of the catalyst $Eu(fod)_3$ in dry $CHCl_3$ inside a sealed-vessel microwave reactor at 60 °C for 2 h afforded a 4:1 ratio of the major *ortho*-rearranged product **5** and the minor *para*-rearranged target compound **3** (entry 1). Extending the reaction time to 4 h, however, produced no significant changes in the composition and yield of the products (entry 2). Given that microwave-accelerated procedure requires a higher temperature to facilitate the tandem Claisen–Cope reaction,[44] we carried out europium(III)-catalyzed rearrangement of 5-*O*-prenyl substrate **4** under microwave irradiation at 100 °C for 30 min. This gave equal amounts of 6-(1,1-dimethylallyl)flavanone **5** and its cyclic derivative **6**, in addition to the major product, 8-prenylated flavanone **3** (entry 3). It is noteworthy that once the 6-rearranged product **5** is formed, the higher temperature enables it to competitively undergo subsequent *para*-Cope rearrangement to provide the 8-prenylflavanone **3**, and to couple with the C-5 hydroxy group to give a diastereomeric mixture of coumaran **6**. To achieve complete *para*-rearrangement, the aforementioned microwave-assisted reaction was allowed to occur for 30 min at 140 °C—the maximum temperature to which the $CHCl_3$ solvent could be



Scheme 1. Preparation of prenyl ether **4**. Reagents and conditions: (a) DEAD, PPh_3, THF, 0 °C to rt, 18 h, 81%; (b) DIAD, PPh_3, THF, MW 60 °C, 30 min, 96%.

Table 1
Results of Claisen rearrangement of compound **4**



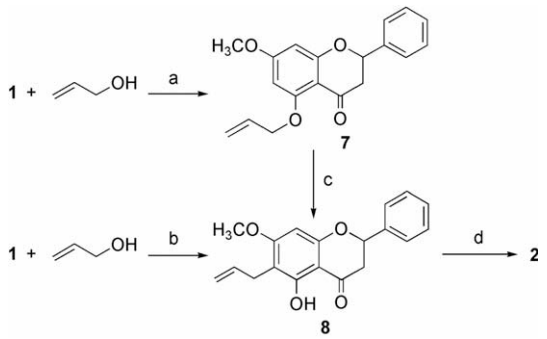
Entry	Microwave heating condition	Yield (%)			
		3	**5**	**6**	Total
1	60 °C, 2 h	18	68	Trace[a]	86
2	60 °C, 4 h	20	63	Trace[a]	83
3	100 °C, 30 min	39	20	27	86
4	140 °C, 30 min	51	0	34	85

[a] The compound was found in only trace amounts.

raised inside the microwave reactor (entry 4). Surprisingly, the 6-allylated product **5** was not detected. The predominant 8-prenyl product **3** occurred in moderate yield along with the minor product dihydrofurano-flavanone **6**.

Next, we sought to execute regioselective C-prenylation at the C-6 position of the lead compound **1** to provide 6-prenylflavanone **2**. The key steps of the synthetic strategy were C-6 allylation via europium(III)-catalyzed Claisen rearrangement, followed by a cross-metathesis (CM) similar to that in previous C-6 prenylations of naringenin and genistein using conventional heating.[51] Unlike the O-prenylation of flavanone **1** described above, we discovered that the classical Mitsunobu procedure using PPh_3 failed to effect the O-allylation of **1**. A previously reported similar reaction on 7,4′-diacetoxy-5-hydroxyflavanone, however, successfully gave the appropriate 5-*O*-allyl derivative.[51] It was assumed that the decrease of the phenolic –OH acidity of compound **1** caused by its 5-methoxy group is responsible for the ineffectiveness of O-allylation described above. We then examined the utilization of another reagent, triisopropylphosphite (TIP), instead of PPh_3. Although the use of TIP gave a moderate yield of allyl ether product **7**, the isopropyl moiety of TIP competitively reacted with the phenolic hydroxyl group to afford isopropyl ether as a side product, which was not easily separated from the major product **7**. Building on the usefulness of the microwave-enhanced Mitsunobu reaction, Moody et al. have realized a microwave-assisted combined Mitsunobu reaction–Claisen rearrangement strategy that enables the rapid synthesis of 1,4-benzoquinone derivatives.[52] Therefore, we sought to apply this combined protocol to our study via the reaction of **1** with allyl alcohol, Ph_3P, and DIAD by heating in dry THF inside the sealed tube of a microwave reactor at 180 °C. After a reaction time of 60 min, however, the corresponding 6-allylpinostrobin **8** was obtained in only 33% yield together with an equal amount of the recovered starting material. Consequently, we settled on a step-by-step synthetic route (Scheme 2) starting with the reaction of flavanone **1** and allyl alcohol under a microwave-assisted Mitsunobu reaction at 60 °C for 30 min to give 5-*O*-allylpinostrobin (**7**) in good yield. The allyl ether substrate **7** was then introduced to a europium(III)-catalyzed Claisen rearrangement in a microwave reactor at 120 °C for 2 h, to obtain C-6 allylated flavanone **8** in good yield. To complete the construction of prenyl functionality, the allyl moiety of **8** was subjected to the CM reaction with isobutylene by using 3 mol % Grubbs catalyst in a sealed tube. The desired 6-prenylflavanone **2** was obtained in high yield after 18 h of standard heating at 45 °C.

The biological activities of all resulting compounds were investigated against a panel of human tumor cell lines including SK-BR-3 (breast), MCF-7 (breast), PC-3 (prostate), and Colo-320DM (colon),[53] as listed in Table 2. The cytotoxicity of the derivatives



Scheme 2. Preparation of 6-prenyl derivative **2**. Reagents and conditions: (a) DIAD, PPh_3, THF, MW 60 °C, 30 min, 71%; (b) DIAD, PPh_3, THF, MW 180 °C, 60 min, 33%; (c) $Eu(fod)_3$, $CHCl_3$, MW 120 °C, 2 h, 70%; (d) $(CH_3)_2C{=}CH_2$, Grubbs catalyst, CH_2Cl_2, sealed tube, 45 °C, 18 h, 85%.

Table 2
Cytotoxicity of compounds **1**–**8** against human tumor cell lines

Compounds	IC_{50} (μM)			
	SK-BR-3	MCF-7	PC-3	Colo-320DM
1	94.3	84.9	86.7	>100
2	30.7	22.9	45.8	52.2
3	34.4	30.3	35.3	24.2
4	19.6	20.3	37.8	37.5
5	12.1	45.6	28.4	36.5
6	14.0	29.5	10.4	18.6
7	24.2	23.9	45.3	37.5
8	18.1	32.2	46.0	68.5

was compared to that of the lead compound **1**. All derivatives exhibited significantly lower IC_{50} values than **1**, and good cytotoxicity against the four cell lines (IC_{50}, 50 μM or lower).[54] The prenyl moieties at the 6-*C*-, 8-*C*-, and 5-*O*-positions of pinostrobin revealed no striking differences in the cytotoxic activity of prenylated derivatives **2**–**4**, respectively, although compound **3** was two times stronger than **2** against Colo-320DM. The *O*-prenyl functionality at C-5 of compound **4** and the *O*-allyl functional group at C-5 of compound **7** provided these compounds with equal cytotoxicity against all cell lines used in this study. A similar phenomenon was also observed when we evaluated the effect of the 6-*C*-prenyl substituent of **2** and the 6-*C*-allyl functional group of **8** on their cytotoxic activities. The 6-(1,1-dimethylallyl) substituent of **5** showed higher cytotoxicity against SK-BR-3, PC-3 and Colo-320DM than the 6-(3,3-dimethylallyl) substituent of **2**. In contrast, compound **2** was two times more active than **5** against MCF-7. The introduction of the allyl or prenyl side chains on an appropriate position of the flavanone structure was found to improve the cytotoxicity. Surprisingly, furo-flavanone **6** was revealed in general to be the most potent inhibitor of all evaluated cell lines due to its hydrophobic dihydrofurano side ring.

In summary, we have developed an efficient microwave-assisted procedure for the allylation and prenylation of pinostrobin (**1**) via the Mitsunobu reaction, *ortho*-Claisen and *para*-Cope rearrangements, and cross-metathesis. Biological evaluations revealed that the two target compounds (**2** and **3**) and five new intermediary substances (**4**–**8**) were more active than the lead compound **1** against a panel of cancer cell lines. The increase of the lipophilicity of the derivatives to interact with biological targets provided by the allyl or prenyl groups can be a basis to explain the improvement of antitumor activity.

Acknowledgments

This research was supported financially in part by a grant for the Open Research Center Project. H.P. thanks Japan Student Services Organization (JASSO) for the Follow-up Research Fellowship, and Indonesian Directorate General of Higher Education (DGHE) for the Competitive Grant Program B (PHK-B).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.02.068.

References and notes

1. Erdtman, H. *Svensk Kemisk Tidskrift* **1944**, *56*, 2.
2. For an example, see: Fang, J. M.; Su, W. C.; Cheng, Y. S. *Phytochemistry* **1988**, *27*, 1395.
3. For an example, see: Kong, Y.; Fu, Y.-J.; Yuan, G.; Liu, W.; Wang, W.; Hua, X.; Yang, M. *Food Chem.* **2009**, *117*, 152.
4. For an example, see: Salvador, M. J.; Sartori, F. T.; Sacilotto, A. C. B. C.; Pral, E. M. F.; Alfieri, S. C.; Vichnewski, W. *Z. Naturforsch., C: Biosci.* **2009**, *64*, 509.

5. For an example, see: English, S.; Greenaway, W.; Whatley, F. R. *Z. Naturforsch., C: Biosci.* **1992**, *47*, 512.
6. For an example, see: Lopez, J. A.; Barillas, W.; Gomez-Laurito, J.; Lin, F.-T.; Al-Rehaily, A. J.; Sharaf, M. H. M.; Schiff, P. L., Jr. *Planta Med.* **1995**, *61*, 198.
7. For an example, see: Morikawa, T.; Funakoshi, K.; Ninomiya, K.; Yasuda, D.; Miyagawa, K.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull.* **2008**, *56*, 956.
8. For an example, see: Portet, B.; Fabre, N.; Rozenberg, R.; Habib-Jiwan, J.-L.; Moulis, C.; Quetin-Leclercq, J. *J. Chromatogr., A* **2008**, *1210*, 45.
9. For an example, see: Cao, C.-M.; Peng, Y.; Xu, L.-J.; Wang, Y.-J.; Yang, J.-S.; Xiao, P.-G. *Chem. Pharm. Bull.* **2009**, *57*, 743.
10. For an example, see: Wachter, G. A.; Wangmaneerat, A.; Caple, K. M.; Montenegro, G.; Timmermann, B. N. *Z. Naturforsch., C: Biosci.* **1999**, *54*, 1140.
11. For an example, see: Vinciguerra, V.; Luna, M.; Bistoni, A.; Zollo, F. *Phytochem. Anal.* **2003**, *14*, 371.
12. For an example, see: Wollenweber, E. *Phytochemistry* **1982**, *21*, 1462.
13. For an example, see: Kamperdick, C.; Hong Van, N.; Van Sung, T. *Phytochemistry* **2002**, *61*, 991.
14. For an example, see: Hao, H.; Handong, S.; Shouxun, Z. *Phytochemistry* **1996**, *42*, 1247.
15. For an example, see: Suga, T.; Iwata, N.; Asakawa, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2058.
16. For an example, see: Cuong, N. M.; Sung, T. V.; Kamperdick, C.; Adam, G. *Pharmazie* **1996**, *51*, 128.
17. For an example, see: Smolarz, H. D.; Mendyk, E.; Bogucka-Kocka, A.; Kocki, J. *Z. Naturforsch., C: Biosci.* **2006**, *61*, 64.
18. Gu, J.-Q.; Wang, Y.; Franzblau, S. G.; Montenegro, G.; Timmermann, B. N. *Z. Naturforsch., C: Biosci.* **2004**, *59*, 797.
19. Wollenweber, E.; Kohorst, G.; Mann, K.; Bell, J. M. *J. Plant Physiol.* **1985**, *117*, 423.
20. Su, B.-N.; Park, E. J.; Vigo, J. S.; Graham, J. G.; Cabieses, F.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *Phytochemistry* **2003**, *63*, 335.
21. Calzada, F.; Velazquez, C.; Cedillo-Rivera, R.; Esquivel, B. *Phytother. Res.* **2003**, *17*, 731.
22. Bohm, B. A. *Biochem. Syst. Ecol.* **1993**, *21*, 745.
23. Wollenweber, E.; Stevens, J. F.; Dorr, M.; Rozefelds, A. C. *Phytochemistry* **2003**, *62*, 1125.
24. Wollenweber, E.; Wehde, R.; Christ, M.; Dorr, M. *Nat. Prod. Commun.* **2008**, *3*, 1285.
25. Hildegard, F.; Zapp, J.; Becker, H. *Phytochemistry* **2003**, *64*, 1335.
26. For a review on propolis, see: Xu, Y.; Luo, L.; Chen, B.; Fu, Y. *Front. Biol. China* **2009**, *4*, 385.
27. Pouget, C.; Lauthier, F.; Simon, A.; Fagnere, C.; Basly, J.-P.; Delage, C.; Chulia, A.-J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3095.
28. Gu, J.-Q.; Park, E. J.; Vigo, J. S.; Graham, J. G.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, *65*, 1616.
29. Wu, N.; Fu, K.; Fu, Y.-J.; Zu, Y.-G.; Chang, F.-R.; Chen, Y.-H.; Liu, X.-L.; Kong, Y.; Liu, W.; Gu, C.-B. *Molecules* **2009**, *14*, 1032.
30. Melliou, E.; Chinou, I. *Planta Med.* **2004**, *70*, 515.
31. Tan, S.-K.; Pippen, R.; Yusof, R.; Ibrahim, H.; Khalid, N.; Rahman, N. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3337.
32. Widianto, M. B.; Satiadarma, K.; Mutschler, E. *Acta Pharm. Indones.* **1986**, *11*, 82.
33. Panthong, A.; Kanjanapothi, D.; Tuntiwachwuttikul, P.; Pancharoen, O.; Reutrakul, V. *Phytomedicine* **1994**, *1*, 141.
34. Yoshikawa, M.; Morikawa, T.; Funakoshi, K.; Ochi, M.; Pongpiriyadacha, Y.; Matsuda, H. *Heterocycles* **2008**, *75*, 1939.
35. Sukardiman; Darwanto, A.; Tanjung, M.; Darmadi, M. O. *Clin. Hemorheol. Microcirc.* **2000**, *23*, 185.
36. Le Bail, J.-C.; Aubourg, L.; Habrioux, G. *Cancer Lett.* **2000**, *156*, 37.
37. Fahey, J. W.; Stephenson, K. K. *J. Agric. Food. Chem.* **2002**, *50*, 7472.
38. Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, U.; Monache, F. D.; Botta, B.; Tomimori, T.; Miyaichi, Y.; Shirataki, Y.; Yokoe, I.; Komatsu, M. *Chem. Pharm. Bull.* **1989**, *37*, 1392.
39. Bobrowska-Hagerstrand, M.; Wrobel, A.; Mrowczynska, L.; Soderstrom, T.; Shirataki, Y.; Motohashi, N.; Molnar, J.; Michalak, K.; Hagerstrand, H. *Oncol. Res.* **2003**, *13*, 463.
40. Li, F.; Awale, S.; Tezuka, Y.; Kadota, S. *Biol. Pharm. Bull.* **2009**, *32*, 2075.
41. (a) Cuca Suarez, L. E.; Delle Monache, F.; Marini Bettolo, G. B.; Menichini, F. *Farmaco* **1980**, *35*, 796; (b) Jayaraman, I.; Ghanim, A.; Khan, H. A. *Phytochemistry* **1980**, *19*, 1267; (c) Rao, P. P.; Srimannarayana, G. *Curr. Sci.* **1981**, *50*, 319.
42. For examples of recent works on **3**, see: (a) Hari Kishore, P.; Vijaya Bhaskar Reddy, M.; Gunasekar, D.; Marthanda Murthy, M.; Caux, C.; Bodo, B. *Chem. Pharm. Bull.* **2003**, *51*, 194; (b) Narvaez-Mastache, J. M.; Garduno-Ramirez, M. L.; Alvarez, L.; Delgado, G. J. *Nat. Prod.* **2006**, *69*, 1687.
43. Braz Filho, R.; Gottlieb, O. R.; Mourao, A. P. *Phytochemistry* **1975**, *14*, 261.
44. (a) Rao, G. S. R. S.; Raghavan, S. *J. Indian Inst. Sci.* **2001**, *81*, 393; (b) Daskiewicz, J.-B.; Bayet, C.; Barron, D. *Tetrahedron Lett.* **2001**, *42*, 7241; (c) Daskiewicz, J.-B.; Bayet, C.; Barron, D. *Tetrahedron* **2002**, *58*, 3589.
45. (a) Gester, S.; Metz, P.; Zierau, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015; (b) Al-Maharik, N.; Botting, N. P. *Tetrahedron* **2003**, *59*, 4177.
46. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
47. (a) Steinreiber, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett.* **2001**, *42*, 6283; (b) Lampariello, L. F.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem.* **2003**, *68*, 7893.
48. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.
49. (a) White, W. N.; Slater, C. D. *J. Org. Chem.* **1961**, *26*, 3631; (b) Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. *J. Org. Chem.* **2003**, *68*, 5493.
50. Yeager, A. R.; Min, G. K.; Porco, J. A., Jr.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065.
51. Tischer, S.; Metz, P. *Adv. Synth. Catal.* **2007**, *349*, 147.
52. (a) Jacob, A. M.; Moody, C. J. *Tetrahedron Lett.* **2005**, *46*, 8823; (b) McErlean, C. S. P.; Moody, C. J. *J. Org. Chem.* **2007**, *72*, 10298.
53. The experimental procedures of synthesis and cytotoxic assay as well as the spectroscopic data of the synthesized compounds are available in the Supplementary data.
54. Boik, J. C.; Newman, R. A. *BMC Pharmacol.* **2008**, *8*, 12 (Open Access: http://www.biomedcentral.com/1471-2210/8/12).