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A One-Pot, Two-Step Synthesis of Tetrahydro Asterriquinone E

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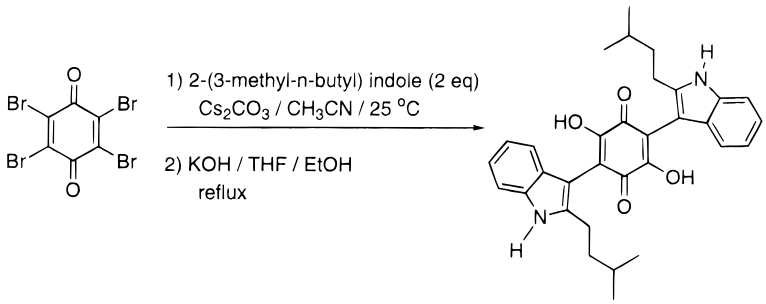
ABSTRACT



Tetrahydro Asterriquinone E

Bis(indolyl)dihydroxyquinone 2, the tetrahydro analogue of naturally occurring 1a, was synthesized by a novel, expeditious route. The short synthesis was accomplished by treating *p*-bromanil (3) with 2 equiv of indole 4 in the presence of cesium carbonate in acetonitrile at ambient temperature to provide a 1:1 mixture of the dibromo regioisomers 7 and 8, followed by hydrolysis of the mixture to afford 2. The synthetic compound 2 was found to inhibit the binding of the Grb2 adapter protein to tyrosine-phosphorylated EGF receptor (IC_{50} = 1.2 μM).

A family of naturally occurring bis(indolyl)dihydroxyquinones, known as asterriquinones, isolated from such fungal strains as *Chaetomium globosum*,[1] *Ch. Cochlioides*,[1] *Ch. murorum*,[2] and *Ch. amygdalisporum*,[2] has been shown to possess a wide array of biological activity.[3] Recently it was discovered in this laboratory that the asterriquinone natural products **1a**−**e** (Scheme 1), isolated from *Aspergillus terreus*, inhibit the binding of Grb2 adaptor protein to tyrosine-phosphorylated EGF receptor (**1a**-IC_{50} = 2.9 μM).[4] The Grb2 inhibitors **1a**−**e** represent the first compounds shown to directly inhibit the interaction between adaptor proteins and protein tyrosine kinase molecules, an interaction implicated in many classes of cancerous tumors.

Despite the therapeutic potential of the natural products **1**,[5] a mild, general synthetic route to these compounds and analogues did not exist in the literature. In view of the potential of compounds **1a**−**e** as anticancer agents, an effort was undertaken to formulate a general synthesis of asterriquinone analogues. In this communication, we describe the novel, expeditious synthesis of the tetrahydro derivative **2** (Scheme 2) of the potent Asterriquinone E[4] (**1a**). Greater

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(1) Brewer, D.; Jerram, W.; Taylor, A. *Can. J. Microbiol.* **1968**, *14*, 861.

(2) Sekita, S. *Chem. Pharm. Bull.* **1983**, *31*, 2998.

(3) (a) Arai, K.; Shimizu, S.; Taguchi, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 991. (b) Shimizu, S.; Yamamoto, Y.; Inagaki, J.; Koshimura, S. *Gann* **1982**, *73*, 642. (c) Kaji, A.; Iwata, T.; Kiriyama, N.; Wakusawa, S.; Miyamoto, K. *Chem. Pharm. Bull.* **1994**, *42*, 1682. (d) Shimizu, S.; Yamamoto, Y.; Koshimura, S. *Chem. Pharm. Bull.* **1982**, *30*, 1896. (e) Ono, K.; Nakane, H.; Shimizu, S.; Koshimura, S. *Biochem. Biophys. Res. Commun.* **1991**, *174*, 56. (f) Brewer, D.; Jerram, W. A.; Taylor, A. U.S. Patent 3917820, 1975. (g) Mocek, U.; Schultz, L.; Buchan, T.; Baek, C.; Fretto, L.; Nzerem, J.; Sehl, L.; Sinha, U. *J. Antibiot.* **1996**, *49*, 854.

(4) (a) App, H.; Fong, A.; Lipson, K.; Harris, D.; Hui, T.; Rice, A.; Wang, H.; Chen, H.; Kim, Y.; Tang, C.; Dare, H.; Margolis, B.; Hirth, P.; Shawver, L.; McMahon, G. *Proc. Am. Assoc. Cancer Res.* **1997**, *38*, 349. (b) Alvi, K.; Pu, H.; Luche, M.; Dare, H.; Margolis, B.; App, H.; McMahon, G. Submitted for publication.

(5) After submission of this paper for publication, an article appeared in which a closely related, naturally occurring asterriquinone is described as an insulin mimetic with antidiabetic activity: Zhang, B.; Salituro, G.; Szalkowski, D.; Li, Z.; Zhang, Y.; Royo, I.; Vilella, D.; Diez, M. T.; Pelaez, F.; Ruby, C.; Kendall, R. L.; Mao, X.; Griffin, P.; Calaycay, J.; Zierath, J. R.; Heck, J. V.; Smith, R. G.; Moller, D. E. *Science* **1999**, *284*, 974.

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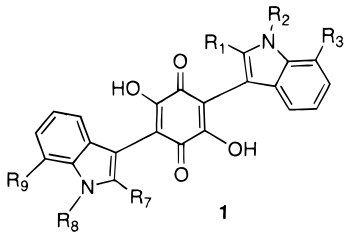
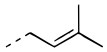
Scheme 1

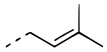


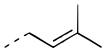
1

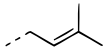
R=H unless otherwise noted

a. R_1=R_7=  (Asterriquinone E)

b. R_2=R_9= 

c. R_1=  R_8= 

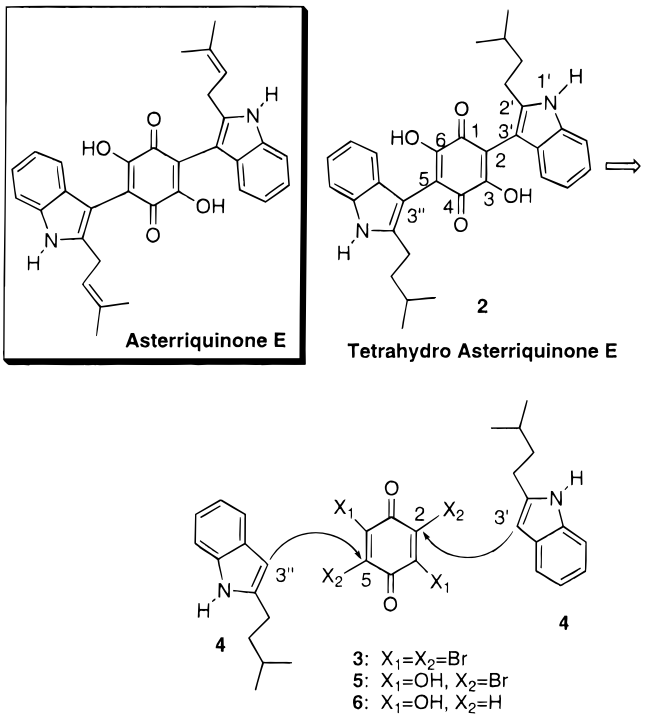
d. R_1= 

e. R_1=R_7=  R_3= CO_2H

ease of synthesis, the presumption of the unimportance of the double bonds of **1a** with regard to activity, and the potential of the olefinic bonds to be metabolized led us to synthesize the tetrahydro derivative rather than the natural product.

Previously published complex, low-yielding syntheses of indolylquinones were inadequate for our purposes.[6,7] In pursuit of an efficient, general methodology for synthesizing asterriquinones, we initially attempted double C−C couplings between 2-(3-methyl-*n*-butyl)indole (**4**)[8] and benzoquinones

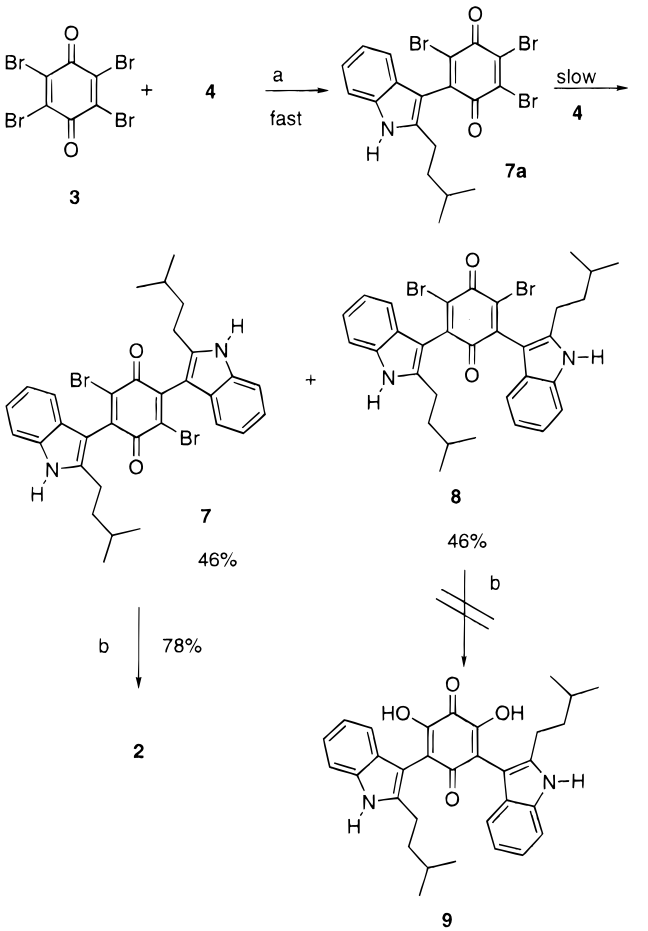
Scheme 2



5 and **6** (Scheme 2). It was hoped that these reactions would provide the bis(indolyl)dihydroxyquinone moiety in one transformation, but in each case, employment of an extensive set of reaction conditions failed to effect the desired indole−quinone coupling. Analysis of the mixture from the reaction between **4** and bromanilic acid (**5**) revealed a bromo-containing bis(indolyl) product, which led us to conclude that an unsymmetrical addition had occurred. This finding prompted us to use the symmetrical quinone *p*-bromanil (**3**).

The synthesis of **2** (Scheme 3) began with commercially available *p*-bromanil (**3**) and indole **4**. Treatment of *p*-bromanil with 2 equiv of **4** in the presence of cesium carbonate in acetonitrile at room temperature afforded a 1:1 mixture of regioisomers **7** (46%) and **8** (44%), separable by flash chromatography.[9] The ^{13}C NMR spectrum of **7** shows only one (C═O) signal, indicative of the *para* regiochemistry. On the other hand, the ^{13}C NMR spectrum of **8** contains two (C═O) signals, indicative of the *meta* regiochemistry. Other combinations of base and solvent were less effective or unsuccessful (Table 1). While the reasons for the improved yield from the Cs_2CO_3/CH_3CN combination are unclear, there are numerous cited examples of improving chemical pro-

Scheme 3[a]



[a] Key: (a) Cs_2CO_3, CH_3CN, 25 °C, 24h; (b) 4N KOH, THF, EtOH, reflux.

Table 1. Indole−Quinone Coupling Conditions for the Generation of **7**

base	solvent[a]	temp, °C	yield, %[b,c]
K_2CO_3	DMF	25	7
	THF	100	3
	THF	50	0
	CH_3CN	50	16
$NaHCO_3$	DMF	100	4
	THF	80	0
	CH_3CN	50	0
Cs_2CO_3	THF	25	0
	DMF	25	17
	CH_3CN	25	28
	CH_3CN	25	46[d]

[a] 0.1 M concentration unless otherwise indicated. [b] An equal amount of *meta* isomer **8** was formed in every case. [c] All reaction times 24 h. [d] 1 M concentration.

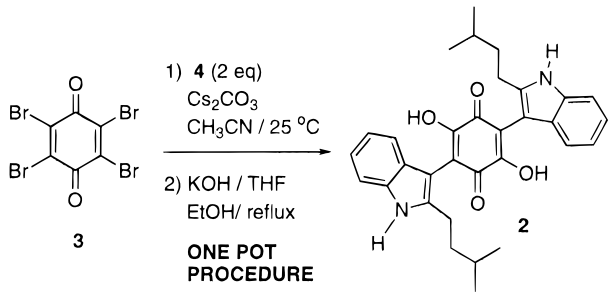
cesses by replacing sodium and potassium compounds with their cesium counterparts.[10]

By monitoring the progress of the reaction via TLC, we discovered that the addition of the first indole to *p*-bromanil to afford the monoadduct **7a** was relatively fast (ca. 2 h) (Scheme 3). In contrast, the addition of the second equivalent of **4** was slow (ca. 22 h). By virtue of this difference between the rates of addition of the first and second equivalents of indole, we were able to synthesize unsymmetrical asterriquinone analogues by adding 1 equiv of one indole to *p*-bromanil followed by addition of an excess of a different indole.[11]

Hydrolysis of *para* isomer **7** with potassium hydroxide produced the bis(indolyl)dihydroxyquinone **2** (78%), found to be slightly more potent against Grb2 function (IC_{50} = 1.2 μM) than the natural product **1a**.[12] Thus, asterriquinone **2** was prepared in two simple steps from commercially available compounds in 36% yield from *p*-bromanil. The activity of **2** indicated that the olefinic functionality present in the indole moiety of **1a** was not necessary for Grb2 inhibition.

Alternatively, the hydrolysis of a mixture of regioisomers **7** and **8** provided pure **2** in 31% yield from *p*-bromanil after HPLC purification (compound **2** was not stable to flash silica or neutral alumina). In this procedure, aqueous KOH and EtOH were added directly to the crude mixture of **7** and **8** in the same reaction vessel without prior workup (Scheme 4). Thus, asterriquinone **2** was synthesized in a simple, *one-pot* transformation in yield equal to the two-step procedure.

Scheme 4



In summary, we have described the short, efficient *one-pot* synthetic route to tetrahydro Asterriquinone E (**2**), the first synthetic substance to directly inhibit the interaction between adapter proteins and protein tyrosine kinase molecules. The promising inhibitory properties of this novel synthetic asterriquinone, as well as its ease of synthesis, highlight the potential of this class of compounds for broad application to the treatment of cancers.

Supporting Information Available: Text giving experimental procedures and spectroscopic data for compounds **2**, **7a**, **7**, and **8** and figures giving the ^{1}H NMR spectrum and an HPLC chromatogram of compound **2** to indicate purity. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990075B

(6) Noland, W. E.; Baude, F. J. *J. Org. Chem.* **1966**, *31*, 3321.
(7) Hoercher, J.; Schwenner, E.; Franck, B. *Liebigs Ann. Chem.* **1986**, *10*, 1765.
(8) Verley, A.; Beduwe, F. *Bull. Soc. Chim. Fr.* **1925**, *37*, 190.
(9) For more examples of Michael-type additions of indoles to quinones, see: (a) Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand., Ser. B* **1976**, *30*, 853. (b) Tsaklidis, J. N.; Hofer, A.; Eugster, C. H. *Helv. Chim. Acta* **1977**, *60*, 1033, 1053. (c) Bu'Lock, J. D.; Harley-Mason, J. *J. Chem. Soc.* **1951**, 703, 710. (d) Bruce, J. M. *J. Chem. Soc.* **1959**, 2366, 2372.
(10) (a) Hofmann, H. *Chem. Ind. Dig.* **1993**, *6*, 113 and references therein. (b) Hofmann, H. *Spec. Chem.* **1993**, *13*, 59, 62−63, 65. (c) Blum, Z. *Acta Chem. Scand.* **1989**, *43*, 248.
(11) Publication in progress.
(12) Hydrolysis of pure **8** under the same conditions gave a complex mixture containing none of the dihydroxy compound **9** (Scheme 3).