COMMUNICATIONS TO THE EDITOR

Short and Convergent Synthesis of Asterriquinone B1 and Demethylasterriquinone B1

Sir:

Asterriquinone B1 (**1**) and its de-*O*-methyl analog, demethylasterriquinone B1 (**2**), which are members of a group of bis-indolyl benzoquinones, were isolated from strains of *Aspergillus terreus*[1] and *Pseudomassaria* sp.,[2] respectively. Especially, the latter product **2** has been reported by Merck group to be the novel insulin receptor activator, that mimics the function of insulin, and therefore, is of potential therapeutic interest for the treatment of diabetes.[2]

The total synthesis of the natural products **1** and **2** has been also accomplished by Merck group using elegant strategies with the rearrangement of pyrandione.[3]

We describe herein a short and convergent synthesis of asterriquinone B1 (**1**) and demethylasterriquinone B1 (**2**).

The construction of **1** and **2** entailed the synthesis of three building blocks, the substituted indols **3** and **5** and the dibromoquinone **4**, as depicted in Fig. 1.

Compounds **3** and **4** were prepared from 2-iodoaniline (**6**) and 2,5-dimethoxy-1,4-quinone (**7**) by the reported processes as shown in Scheme 1.[4,5]

The C2 substituted indol **5** was synthesized by chlorination of indol (**8**) with NCS to give 3-chloroindol (**9**), followed by treatment of prenyl-9-BBN.[6]

Reaction of **4** with the lithiated **5** gave selectively the mono-substituted **10** without substitution of the bromide in 61% yield. This reaction seemed to proceed apparently in the Michael-retro Michael type based on the stability of the produced anion between the carbonyl and bromo groups.

Another indol moiety was further introduced onto **10** by using the lithiated **3** to afford the disubstituted **11** in 72%.

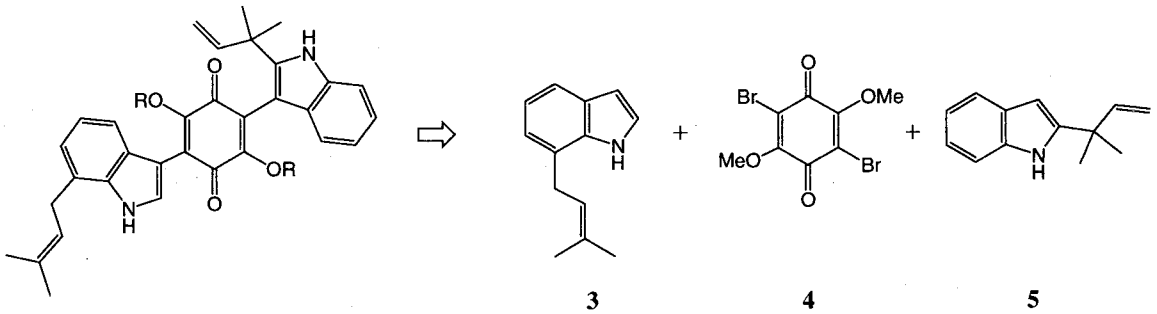
The synthesis was completed as follows. A solution of **11** in a mixture of dioxane and aq KOH solution was refluxed for 2 hours. After neutralization with Dowex 50WX8 (H type) and filtration, the filtrates were evaporated to the residue, which was chromatographed on silica gel [silica gel 60 (acidic), Kanto Chemicals] with PhMe - EtOAc (20 : 1) to give purple solids of **2** and **12** in 30% and 18% yields, respectively [on TLC (PhMe - EtOAc - AcOH=25 : 5 : 1), **2**: Rf 0.23; **12**: Rf 0.56]. Recrystallization of **2** from EtOAc-hexane gave purple needles: mp. 204°C (change of color at about 92°C).[2] The synthetic product **2** was identical in all respects with natural demethylasterriquinone B1.[2,3]

The structure of the mono-bromide **12**, which was isolated as a single isomer, was determined mainly by NMR studies as shown in Scheme 1.

Alternatively, **2** was obtained from asterriquinone B1 (**1**) by de-*O*-methylation with aq KOH in EtOH in 78% yield.[7]

Asterriquinone B1 (**1**) was synthesized in 74% yield from **11** by treatment with NaOH in MeOH for 4 hours. Recrystallization from benzene gave purple prisms of **1**: mp 211~213°C (change of color at about 112°C), which was

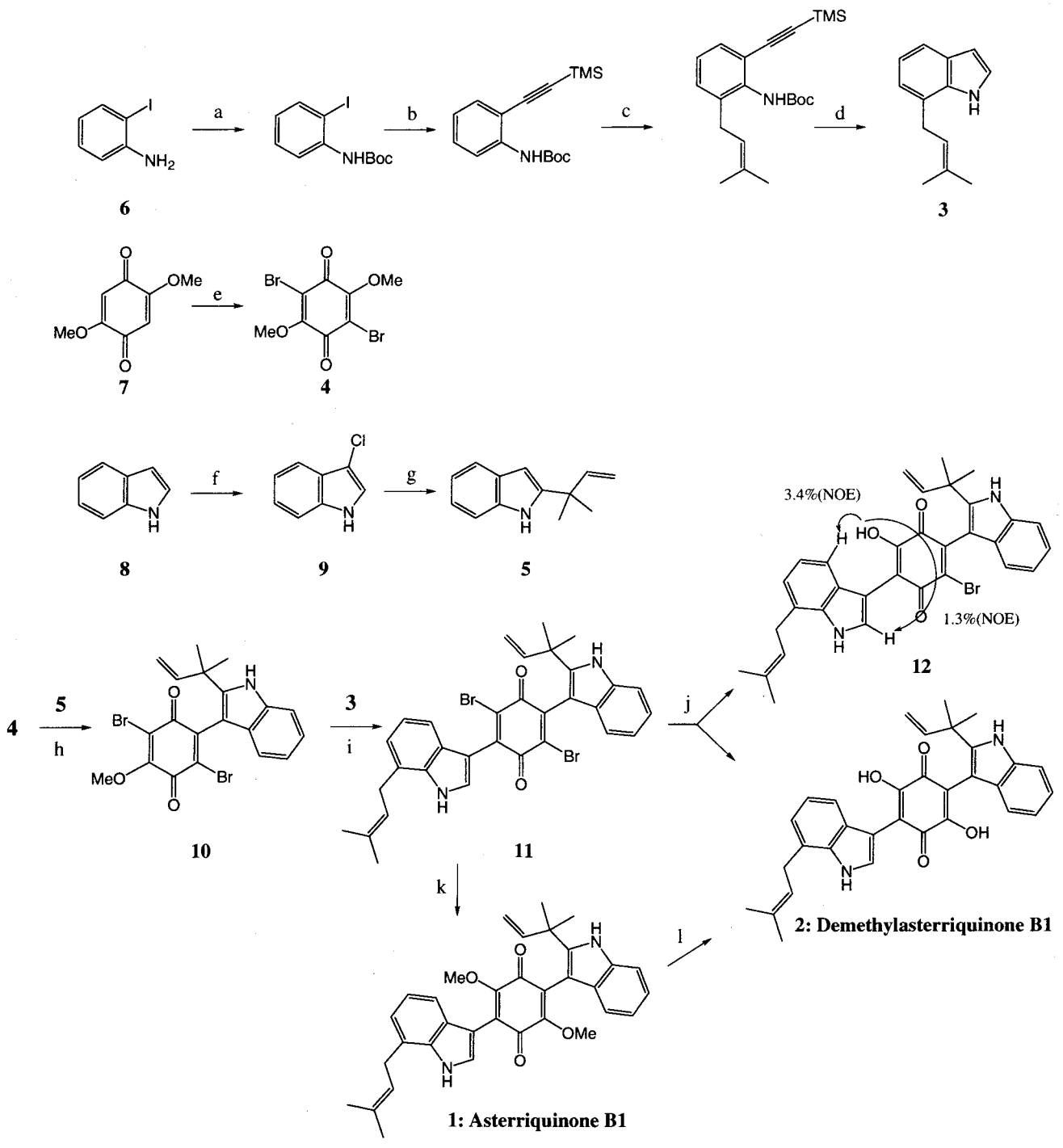
Fig. 1.



3 **4** **5**

1: Asterriquinone B1: R=Me
2: Demethylasterriquinone B1: R=H

Scheme 1.



Conditions; (a) $(Boc)_2O$, *i*-Pr_2NEt/THF, 80°C, 5 days; 86% (b) (Trimethylsilyl)acetylene, $Pd(PPh_3)_2Cl_2$, CuI/Et_3N, rt, 40 minutes; 88% (c) *t*-BuLi/Et_2O, -20°C, then 4-bromo-2-methyl-2-butene, -78°C to rt, 5 hours; 86% (d) NaOEt/EtOH, reflux, 7.5 hours; 76% (e) Br_2 on Al_2O_3, sonicator, rt, 2 days; 51% (f) NCS/CCl_4, 0°C, 1 hour; 82% (g) Prenyl-9-BBN, Et_3N/THF, rt, 12 hours; 72% (h) LiN$(TMS)_2$/THF, -78°C to rt, 3 hours; 61% (i) *s*-BuLi/THF, -78°C to rt, 2 hours; 72% (j) aq. KOH/dioxane, reflux, 2 hours; 30% of **2** (k) NaOH/MeOH, rt, 4 hours; 74% (l) aq. KOH/EtOH, reflux, 2 hours; 78%

Table 1. Physico-chemical properties of compounds.

Compds.	Mp (°C)	^{1}H-NMR (400, 500 or 600MHz; δ ppm; *J* Hz) ^{13}C-NMR(125MHz; δ ppm)
1	211-213 (change of color at ~112°C) prisms (from benzene)	^{1}H-NMR($CDCl_3$): δ 1.48(6H, s), 1.79(3H, s), 1.83(3H, s), 3.60(2H, d, *J*=7.0Hz), 3.68(3H, s), 3.79(3H, s), 5.13(1H, dd, *J*=10.6&1.0Hz), 5.18(1H, d, *J*=17.4&1.0Hz), 5.40-5.47(1H, m), 6.09(1H, dd, *J*=17.4&10.6Hz), 7.02-7.16(4H, m), 7.26(1H, d, *J*=8.0Hz), 7.31(1H, d, *J*=8.0Hz), 7.40(1H, d, *J*=8.0Hz), 7.56(1H, d, *J*=2.8Hz), 8.12(1H, br s), 8.52(1H, br s) ^{13}C-NMR($CDCl_3$): δ 18.0, 25.7, 26.8, 27.1, 30.8, 39.3, 60.0, 60.7, 77.2, 101.7, 105.8, 110.6, 112.3, 118.7, 119.3, 120.2, 120.6, 120.7, 121.9, 122.0, 122.2, 124.1, 126.7, 127.4, 129.8, 133.6, 134.5, 135.0, 142.1, 145.4, 154.4, 156.3, 183.5, 184.0
2	203-204 (decomp.) (change of color at ~92°C) needles (from EtOAc-hexane)	^{1}H-NMR($(CD_3)_2CO$): δ 1.52(6H, s), 1.75(3H, s), 1.77(3H, s), 3.64(2H, d, *J*=7.0Hz), 5.00(1H, dd, *J*=10.4&1.0Hz), 5.09(1H, dd, *J*=17.0&1.0Hz), 5.44-5.51(1H, m), 6.16(1H, dd, *J*=17.0&10.4Hz), 6.91-7.06(4H, m), 7.28(1H, d, *J*=7.8Hz), 7.32(1H, d, *J*=7.8Hz), 7.44(1H, dd, *J*=7.0&1.0Hz), 7.62(1H, d, *J*=3.0Hz), 9.40(1H, br s), 10.07(1H, br s), 10.43(1H, br s) ^{13}C-NMR($CDCl_3$): δ 18.0, 25.7, 26.9, 30.8, 39.3, 99.5, 104.7, 110.7, 111.0, 111.7, 112.3, 118.6, 119.8, 120.0, 120.5, 122.1, 122.2, 122.2, 124.2, 126.0, 126.7, 128.2, 128.5, 129.0, 133.6, 134.7, 135.2, 142.5, 145.5
10	58-60 prisms (from benzene)	^{1}H-NMR($(CD_3)_2CO$): δ 1.45(6H, s), 4.23(3H, s), 5.02(1H, dd, *J*=11.0&1.0Hz), 5.04(1H, dd, *J*=18.0&1.0Hz), 6.05(1H, dd, *J*=18.0&11.0Hz), 6.94(1H, dd, *J*=8.0&8.0Hz), 7.06(1H, dd, *J*=8.0&8.0Hz), 7.19(1H, d, *J*=8.0Hz), 7.34(1H, d, *J*=8.0Hz), 10.36(1H, br s) ^{13}C-NMR($CDCl_3$): δ 26.8, 27.7, 39.3, 62.0, 105.5, 110.9, 113.2, 118.7, 119.4, 120.3, 122.4, 126.5, 134.8, 134.8, 142.3, 145.1, 145.5, 156.5, 174.5, 177.7
11	213-215 (decomp.) needles (from EtOAc-hexane)	^{1}H-NMR($(CD_3)_2CO$): δ 1.48(6H, s), 1.73(3H, s), 1.75(3H, s), 3.64(2H, d, *J*=7.0Hz), 5.06(1H, dd, *J*=11.0&1.0Hz), 5.09(1H, dd, *J*=18.0&1.0Hz), 5.42-5.47(1H, m), 6.09(1H, dd, *J*=18.0&11.0Hz), 6.91-7.07(5H, m), 7.27(1H, d, *J*=8.0Hz), 7.34(1H, d, *J*=8.0Hz), 7.67(1H, d, *J*=3.0Hz), 10.37(1H, br s), 10.80(1H, br s) ^{13}C-NMR($CDCl_3$): δ 18.0, 25.7, 26.8, 27.7, 30.7, 39.3, 106.0, 109.4, 110.9, 113.2, 118.8, 119.8, 120.3, 121.0, 122.0, 122.3, 122.5, 124.7, 125.0, 126.6, 128.6, 133.2, 133.9, 134.8, 135.0, 137.3, 141.9, 142.0, 145.2, 145.7, 177.6
12	107-110 needles (from EtOAc-hexane)	^{1}H-NMR($(CD_3)_2CO$): δ 1.52(6H, s), 1.76(3H, s), 1.78(3H, s), 3.65(2H, d, *J*=7.0Hz), 5.01(1H, d, *J*=10.4Hz), 5.11(1H, d, *J*=17.0Hz), 5.42-5.53(1H, m), 6.17(1H, dd, *J*=17.0&10.4Hz), 6.90-7.08(4H, m), 7.28(1H, d, *J*=7.8Hz), 7.33(1H, d, *J*=7.8Hz), 7.45(1H, br d, *J*=7.0Hz), 7.62(1H, d, *J*=3.0Hz), 10.10(1H, br s), 10.46(1H, br s) ^{13}C-NMR($CDCl_3$): δ 18.0, 25.7, 26.8, 27.6, 30.7, 39.3, 104.7 105.8, 110.9, 113.0, 115.7, 118.6, 119.9, 120.3, 120.6, 122.2, 122.3, 122.4, 124.2, 125.9, 126.7, 128.0, 133.6, 134.9, 135.1, 141.2, 141.8, 141.9, 145.2, 149.0, 179.4, 180.9

identical in all respects with the natural product.[1,3]

At the heart of the synthesis described herein is the selective introduction of two different components **3** and **5** onto the benzoquinone core **4**.

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References

1) YAMAMOTO, Y.; K. ARAI, K. MASUDA, N. KIRIYAMA, K. NITTA & S. SHIMIZU: Metabolic products of *Aspergillus terreus*. IV. Metabolites of the strain IFO 8835. (2). The isolation and chemical structure of indolyl benzoquinone pigments. Chem. Pharm. Bull. 29: 961~969, 1981
2) WOOD, H. B. Jr.; R. BLACK, G. SALITURO, D. SZALKOWSKI, Z. LI, Y. ZHANG, D. E. MOLLER, B. ZHANG & A. B. JONES: The basal SAR of a novel insulin receptor activator. Bioorg. Med. Chem. Lett. 10: 1189~1192, 2000
3) LIU, K.; H. B. WOOD & A. B. JONES: Total synthesis of asterriquinone B1. Tetrahedron Lett. 40: 5119~5122, 1999
4) KONDO, Y.; S. KOJIMA & T. SAKAMOTO: A concise synthesis of 7-substituted indoles. Heterocycles 43: 2741, 1996
5) KHANNA, R. N.; V. BANSAL, S. KANODIA & P. C. THAPLIYAL: Microwave induced selective bromination of 1,4-quinones and coumarins. Synth. Commun. 26: 887~892, 1996
6) SCHKERYANTZ, J. M.; J. C. G. WOO & S. J. DANISHEFSKY: Total synthesis of gypsetin. J. Am. Chem. Soc. 117: 7025~7026, 1995
7) YAMAMOTO, Y.; K. ARAI, S. SHIMIZU & Y. TAGUCHI: Metabolic products of *Aspergillus terreus*. V. Demethylation of asterriquinones. Chem. Pharm. Bull. 29: 991~999, 1981

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